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AN UNUSUAL VARIANT OF ACUTE IDIOPATHIC POLYNEURITIS (SYNDROME OF OPHTHALMOPLEGIA, ATAXIA AND AREFLEXIA)*

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THE purpose of this communication is to report 3 cases of an acute neurologic illness characterized among other features by total external ophthalmoplegia, severe ataxia and loss of the tendon reflexes. The clinical picture in all 3 cases was so similar as to constitute an easily recognizable syndrome. The presenting symptoms and signs were most alarming for the attending physician on each occasion — unnecessarily so, since the course of the illness appears to be benign. The cause of the syndrome was obscure until, in the most recent case, a great rise in the protein of the cerebrospinal fluid in the late stages of the illness indicated a close relation to the Guillain–Barré type of polyneuropathy. Although it is therefore likely that the illness under discussion is but another variant of so-called infective polyneuritis in which limb involvement is minor, the diagnosis is hardly to be suspected at the onset unless one realizes that such an atypical form exists. Moreover, several features of the neurologic disturbance are worthy of emphasis — for example, the striking symmetry of the ocular palsies and the severity of the ataxia. For these reasons it is considered worth while to call attention to this interesting though rare condition.

Several different terms have been used for the type of polyneuropathy referred to herein, such as Guillain–Barré syndrome, acute infective polyneuritis, acute febrile polyneuritis of Osler and acute idiopathic polyneuritis. The last of these is used here in preference to the others.

CASE REPORTS

CASE 1. G.E.M. (M.G.H. 189834), a 45-year-old man, was transferred to the Massachusetts General Hospital with total external ophthalmoplegia and severe ataxia.

Neurologic complaints had begun 4 days previously, but the patient recalled that he had had a mild sore throat about 4 days before that. He had been in another hospital for 3 days. On the 1st day of illness, a slight transient dizziness had been noted — not a rotational feeling, but an unsteady sensation in the head. Later in the day there was a feeling of malaise, and the chest felt as if it were tightening up "like an ordinary cold." About 4 p.m., on trying to climb a stepladder, he noted that the unsteady feeling in the head had become worse. When he awoke the next morning his head "felt like a balloon," and on going to the bathroom, he walked "like a drunken sailor." The feet tended to lift up very lightly like feathers and could not be placed properly on the floor again but instead plopped down. The dizziness in the head seemed distinct from this disturbance of gait. At some time during the 2d day horizontal diplopia appeared on near vision, but not for distant objects. Vision was not as distinct as usual. In the evening the fingers of both hands became numb, and the arms felt sore and lame. The lower limbs were not affected. The tightness in the chest, which had become worse, was situated deep and centrally, directly behind the lower sternum. A mild, deep cough had appeared, and coughing produced a sharp, splitting pain in the midfrontal region. The patient did not use alcoholic beverages and had been taking a well balanced diet up to the onset of his illness.

At the 1st hospital, examination by Dr. Robert K. Davis, on the 3d day of illness, showed paralysis of abduction of the right eye and questionable impairment of the 4th nerve. The pupils were large and reacted only slightly to light. The deep tendon reflexes were hypoactive (the patient thought they had always been so), and there was marked ataxia on the finger-nose and heel-knee tests. Flexion of the right arm was weak. The temperature was 99°F., and the blood pressure 120/76. Examination of the blood and urine was not remarkable. The blood Wassermann test was negative. The cerebrospinal fluid examined on admission was clear, and contained 1 lymphocyte per cubic millimeter. The sugar was 72 mg., and the protein 36 mg. per 100 ml. The pressure was equivalent to 165 mm. of water. During the following 2 days the picture worsened, ophthalmoplegia, ataxia and weakness all increasing, and the patient was transferred to the Massachusetts General Hospital.

On admission the chief complaint was ataxia, which was so severe in the arms that eating was precluded, and in the legs of such a degree that he had to be supported in walking. Mild diplopia was present, but this seemed to disturb him very little, in view of the total ophthalmoplegia (described below). The fingers felt numb, but not the face or feet. He had a deep-seated headache that was particularly aggravated by coughing. Another important complaint was the tight feeling in the chest behind the sternum. There was no associated shortness of breath. He thought his limbs were weak, but this was more subjective than objective.

His mind was lucid; there was no drowsiness, and the history was given without difficulty. The ocular findings were most striking. There was a complete external ophthalmoplegia and an almost complete internal ophthalmo-

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plegia. The eyes were fixed in the normal forward-gaze position, and the axes were aligned, not askew. The pupils were equal and measured 5 mm., and both reacted only sluggishly to light. The eyeballs did not move voluntarily or reflexly. Bell's phenomenon was absent. Rotation of the head produced no change in the position of the eyes. However, ptosis was only moderate in degree, and levator function was good when he attempted to look up. Blinking was normal. Visual acuity, the visual fields and the fundi were not remarkable. Corneal sensation was intact. Function of the orbicularis oculi was excellent, as was that of the rest of the facial musculature. However, the patient had considerable difficulty in chewing meat for the 1st few days, and this in retrospect was probably significant. Hearing was normal. Swallowing, speaking and enunciation were not remarkable, except that toward the end of the interview some hoarseness appeared. The palate was elevated in the mid-line; the tongue was protruded normally, and sternocleidomastoid power was good.

Motor power in the limbs approached normal, and whereas some observers believed that there was no significant weakness, others found mild weakness of the forearm flexors bilaterally, winging of the scapulas and diminished strength in the abductors of the thigh. The patient had had poliomyelitis as a child, and as a sequela the left foot had remained wasted and deformed.

Sensation for light touch, position and number writing was normal. Vibration sense was strikingly impaired, being entirely absent in the lower limbs as well as over the trunk below the 4th thoracic dermatome and diminished in the hands. Pinprick sensation was mildly impaired on the dorsum of the feet.

All tendon reflexes were absent. The plantar responses were briskly flexor. A most severe ataxia of a rhythmic type was present on the finger-nose and heel-knee tests bilaterally. While he was sitting, titubation of the trunk was so marked that the patient literally bobbed around. The gait was not tested since he could scarcely stand because of the ataxia. The following diagnoses were among those suggested: basilar-artery occlusion; atypical Wernicke's disease; polyneuritis; multiple sclerosis; brain-stem tumor; poliomyelitis (an epidemic was in progress at the time); and trichinosis.

Examination of the blood and urine was not remarkable. The sedimentation rate was 4 mm. in 1 hour. Roentgenograms of the skull and chest were normal. The cerebrospinal fluid was under a pressure equivalent to 135 mm. of water and was crystal clear. A cell count showed 5 lymphocytes and 8 red blood cells per cubic millimeter. The total protein was 68, and the sugar 97 mg. per 100 ml., and the colloidal-gold curve 0000000000. The spinal-fluid Wassermann test was negative. Porphobilinogen was not found in the urine. The electroencephalogram was mildly abnormal because of some alpha flattening in the left occipital region. Dr. Maurice Victor kindly determined the blood pyruvate and lactate levels, finding both mildly but significantly elevated in the fasting state; in addition the tolerance curve for each was abnormally high.

The patient remained in the hospital for 32 days and showed steady improvement, as described below. On the 30th day of the illness a repeat examination of the cerebrospinal fluid again showed crystal-clear fluid, but the total protein had risen to 348 mg. per 100 ml.

Four days after admission and on the 8th day of illness, he already felt better but pain across the neck and shoulders posteriorly persisted. Ptosis was less, and the pupils reacted more briskly to light. Very slight conjugate downward movement of the eyes was already possible. Ataxia was still severe, and when the palms were pressed together to test the power in the pectoral muscles, the arms "flipped" uncontrollably up and down, once striking the patient forcefully in the face. Chewing movements were much better. By the 13th day of illness remarkable improvement had occurred in several respects. The numbness was for the most part gone from the hands, and vibration sense was well appreciated in the fingers and toes. The other modalities of sensation had also returned to normal. Ataxia had decreased, and the patient could walk around the room holding on to the furniture. The Romberg test was negative. Downward conjugate gaze was co-ordinated and of almost full range. Conjugate lateral movements were restricted to a few degrees to the left and about the same to the right. Bell's phenomenon was now present. The pupils were smaller and reacted very briskly to light. Ptosis had cleared. This degree of improvement occurred without any drug or vitamin therapy. During the next few days a complete left-sided facial palsy of the peripheral type appeared abruptly. Taste was absent on the anterior part of the left side of the tongue, indicating that the facial-nerve lesion was not situated far peripherally.

Examination on the 24th day of illness showed definite improvement in the facial weakness. The eyes seemed unusually prominent, and because of this the protein-bound iodine was determined and found to be within normal limits. The eyes moved downward well, about 150° to the right and minimally to the left. Vertical movement was not obtained. Convergence was excellent. After careful testing it was concluded that the ocular movements that were present were conjugate, as far as could be judged grossly. Diplopia was present but was not troublesome. The tendon reflexes were still absent; the plantar responses were flexor. The ataxia of the limbs was now only moderate, and the patient could walk unaided. Sensory testing revealed no deficit. The limbs were probably still slightly weak. By the 29th day conjugate lateral gaze was much improved to both sides, but did not approach normal by any means. Gaze was approximately conjugate, but abduction of each eye was a little better than adduction. The shoulder and pelvic-girdle muscles still had not regained normal strength.

The patient was discharged from the hospital, and examination 6 weeks after the onset of the illness showed further remarkable improvement. There was no ptosis. Diplopia was present only at distances greater than 46 cm. On conjugate lateral gaze, the adducting eye moved inward fully, but the abducting eye failed to obliterate the white of the sclera by about 3 mm. Downward gaze was full, and convergence was normal. Vertical gaze had definitely begun to return but was still much restricted. The impairment of eye movements was strikingly symmetrical. There was no nystagmus. The pupils reacted normally to light and on accommodation. The tendon reflexes were still absent except perhaps for the triceps jerks. Sensation in all limbs was excellent. The left-sided facial paralysis had completely disappeared. Ataxia was minimal. Twelve weeks after the onset of the illness the patient reported that when he arose in the morning, vision was perfect but that later in the day objects became fuzzy at a distance. He could read figures all day perfectly. The arms still seemed to tire excessively. On examination ocular movements were full except for slight restriction of abduction bilaterally, and this was associated with horizontal nystagmus, which was greater in the abducting eye than in the adducting one, mimicking the picture of partial internuclear ophthalmoplegia. Testing with the red glass showed an uncrossed diplopia with 2.5-cm. separation of the images at a distance of 1 meter that was approximately equal in all fields.

In this case, over a four-day period, severe ataxia, complete external ophthalmoplegia and almost complete internal ophthalmoplegia, tightness in the chest and numbness of the fingers developed. Recovery began on the eighth day of illness, with improvement in the pupillary reaction and the return of rather good conjugate gaze downward. Within two weeks the sensory deficit had cleared, and the ataxia had diminished. At the end of six weeks eye movements were full except for abduction, which was slightly restricted bilaterally. The tendon reflexes remained absent. The spinal-fluid protein, which was at first 36 mg., rose to 38, 68 and finally to 348 mg. per 100 ml. thirty days after the onset, establishing the illness as probably related to infective polyneuropathy of the Guillain–Barré type.

CASE 2. E.L., a 63-year-old man, was admitted to the Royal Victoria Hospital, Montreal, Canada, in October, 1949, complaining of malaise, fever (temperature of 102°F.) and cough of 2 weeks' duration. On examination, he was dyspneic and slightly cyanosed, and rales were present at both lung bases. The blood pressure was 210/110. There was a history of a definite posterior myocardial infarction in 1947, with subsequent mild shortness of breath on exertion. A roentgenogram of the chest showed pneumonitis. *Haemophilus influenzae* was cultured from the sputum. The blood Wassermann test was negative. Procaine penicillin, 300,000 units a day, was given intramuscularly, and clinical progress was slow, although the temperature fell to normal after 24 hours. Streptomycin, 0.5 gm. intramuscularly twice each day, was administered in addition for 11 days starting on the 2d hospital day. On the 14th hospital day the patient was not as alert as usual, slept for long periods and was unable to feed himself because of unsteadiness of the hands. At the same time burning and tearing of the eyes appeared, with "frosting of vision." He was unable to read. Ataxia was so severe that "the ward was not wide enough for me to walk." There was no dizziness and no diplopia. He later thought that the symptoms had developed slowly over a period of 1 week; at least they came on gradually.

On the 16th hospital day he was examined by Dr. Arthur Young, who noted that the eyes were fixed in the mid-line and that there was absolutely no movement of either eye. The lids were retracted rather than ptosed, and the eyes appeared prominent. When the lids were closed the eyes did not roll up. The pupils were equal and reacted very sluggishly to light. Convergence and accommodation were absent. In spite of early cataract formation bilaterally the fundi and disks were normal except for Grade 1 hypertensive changes. The remainder of the cranial nerves were normal. All tendon reflexes were absent; the abdominal reflexes were active, and the plantar responses were flexor.

There was no paralysis or weakness. Marked inco-ordination of all extremities was present but especially of the left arm and leg. This was thought to be cerebellar in type. There was no sensory impairment to pain, vibration or position. A roentgenogram of the skull was normal. The cerebrospinal fluid was not examined. There had been no recognized nutritional disturbance, and the patient was not an alcoholic.

Within a few days he was quite bright again and was allowed up. At the end of 1 week he could see to read. Ocular movements returned slowly, and 2 weeks after the recognized onset — that is, on the 28th hospital day — the right eye was still immobile whereas the left could be adducted but not abducted. Balance was better, and he could walk by himself. There had been no special therapy.

At the end of 5 weeks it was recorded that he complained only of some instability on walking. Visual acuity was good. The visual fields were full. There was mild ptosis on the right. "Some impairment" of upward and lateral gaze in each eye was still present. The left pupil was a little larger than the right. The pupils reacted to light and on accommodation. No nystagmus was noted. Motor power, co-ordination and sensation were within normal limits. The tendon reflexes were present and equal except for the left ankle jerk, which was still absent. He could walk in a straight line with the eyes open and closed, but a mild degree of ataxia on walking could be noted. Two weeks later no abnormal neurologic signs remained. On examination in 1953, 4 years later, there were no residual signs. The tendon reflexes were active.

This patient, who was admitted to the hospital for a respiratory infection, was progressing well when, two weeks after admission, complete ophthalmoplegia, mild drowsiness, severe ataxia and loss of the deep reflexes developed. Without special therapy, recovery began in a few days and was relatively complete in seven weeks.

CASE 3. T.W.O., a 63-year-old man, had had several previous admissions to the hospital for bronchial asthma, chronic bronchitis, pulmonary emphysema and mild cardiac failure. On May 6, 1953, he was readmitted to the Queen Mary Veterans Hospital, Montreal, Canada, complaining of increased cough, sputum and shortness of breath for 7 days. Physical examination showed a poorly nourished, gaunt man who appeared acutely ill. The temperature was 101°F., the pulse 120, and the respirations 22. He was moderately dyspneic, and rales were present at the right-lung base. There were no signs of cardiac failure. The blood pressure was 175/100. A roentgenogram of the chest showed no change from previous films. A diagnosis of pneumonitis was made, and procaine penicillin, 300,000 units intramuscularly twice a day, was administered. In addition, Neo-Synephrine aerosol, aminophylline and phenobarbital were prescribed. The fever quickly disappeared, and the patient was remarkably improved within a few days.

On May 13 a severe bilateral headache that seemed to be present on awakening and improved after a cup of tea first developed. On the next day diplopia was noted on distant but not on near gaze. Examination was not remarkable. On May 15 he still complained of headache and diplopia, and examination revealed the pupils to be equal, rather dilated and responding sluggishly to light. Convergence was somewhat impaired. The deep reflexes seemed diminished. There was no nystagmus, inco-ordination or sensory deficit. By May 16 bilateral "6th-nerve" paralysis, slight rotatory nystagmus on attempted lateral gaze, absent deep reflexes and a wide-based ataxic gait had appeared. Morning headache continued. The patient told 1 examiner that for 1 week he had had sensations of pins and needles in the tips of the fingers but not in the toes. The fingers tingled when he touched them. On May 17 there was a bilateral 6th-nerve palsy but good ocular movements upward and downward. Bilateral ptosis had been added to the picture. Neostigmine, 1.5 mg intramuscularly, had no effect on the eye movements. Ocular movements became further impaired by May 19, when the patient still had a headache upon coughing. He no longer complained of diplopia but rather of blurred vision. In general he felt well. His mind was clear, and his memory intact; there was no drowsiness or confusion. He co-operated well in all the tests.

The eyes at rest were in the normal forward-gaze position without any skew. There was moderate ptosis bilaterally. Ocular movements were greatly impaired, with absolutely no movement conjugately or individually of either eye, laterally, medially, upward or on convergence. However, gaze downward was well performed, and Bell's phenomenon was still present. (On the previous day 1 examiner had found no ocular movement at all.) Head turning and nodding did not influence eye movement. Random movements were absent, and the possibility of apraxia was ruled out. The pupils were large (4 mm.) and reacted only slightly to light. Nystagmus was absent. The fundi were not remarkable, and the visual fields were full on confrontation. The visual acuity was 20/30 bilaterally. Facial movements were all strong, including eye closing. Hearing was normal, as was examination of the throat and tongue. There had not been dysarthria or dysphagia at any time.

Motor power in the arms and legs was good. Sensation for pinprick, touch, vibration, position and fine discrimination was within normal limits. Rapid alternating movements of the hands were well performed, but on the finger-nose test there was a fine, rhythmic terminal tremor especially on the left. The heel-knee test showed no abnormality, but the gait was broad-based and reeling. (The patient was certain that this had been present only a few days.) All tendon reflexes were absent, and the plantar responses were flexor. The blood pressure was 175/100.

Inquiry disclosed that he had been eating adequately and had gained 0.5 kg. (1 pound) since admission. Although he was thin there had been no appreciable weight change in the previous 2 years. No unusual drugs had been administered. Penicillin had been given for 8 days (a total of 4,800,000 units).

Laboratory studies were normal for the most part. Urinalysis and blood count were not remarkable except for a raised sedimentation rate. The cerebrospinal fluid, which was clear and colorless, was under an initial pressure equiva-

lent to 100 mm. of water and showed 1 polymorphonuclear leukocyte and 1 lymphocyte. The protein was 35 mg. per 100 ml. Six weeks later the cerebrospinal fluid was unchanged, including the protein. Blood and spinal-fluid Wassermann tests were negative. Roentgenograms of the skull were within normal limits, as was the electroencephalogram. Sputum cultures taken on admission showed a moderate growth of *H. influenzae*. Electrocardiographic abnormalities had been noted previously and had changed but little.

For a few days after May 19 there was little change, and headache continued. On May 25 the pupillary response to light was slightly better, and the brachioradialis reflexes were +++. By May 27 movement of the eyes was beginning to reappear, with minimal function upward, laterally and on convergence. The pupillary reflex was now brisk, and only slight ptosis persisted. There had been no drug therapy at all. Progress was slow, and on June 9 (27 days after the onset), gross ocular paresis was still evident, although definite improvement had occurred. Gait was no longer ataxic, and Romberg's sign was absent. By June 12 there had been very definite improvement in eye movements, and the tendon reflexes in the lower limbs had now returned. The knee and ankle jerks were ++. The blood pressure ranged from 180/90 to 180/104. A trial of vitamin B_{12}, 1 mg. per day, was started, but after 5 days no dramatic response had occurred. Improvement thereafter was gradual, and 3 months after the onset, ocular movements were virtually intact, including convergence, but the patient complained of a horizontal diplopia for reading and used a shield over the left eye. Gait and reflexes were normal. There was no nystagmus. In the following 12 months no appreciable change took place, diplopia persisting and being made worse by lateral gaze. On examination eye movements were grossly normal.

In this case a severe external and internal ophthalmoplegia (downward gaze may have been spared) developed, as well as ataxia over a period of six days associated with headache and loss of the tendon reflexes. No cause for the illness could be found. Ocular movements began to return in six days and were full on gross testing three months later, but horizontal diplopia was still present a year later. The pupillary reflexes returned in about a week. Ataxia had cleared in three weeks or earlier, and the tendon reflexes had returned in about the same period.

The Clinical Picture

Table 1 summarizes the cases presented above. Case 3 was the first seen personally, and although no diagnosis was made, a rise in the cerebrospinal-fluid protein was looked for at the end of six weeks, since the transient numbness of the fingers and the loss of the tendon reflexes had suggested a polyneuropathy. The protein was normal, and the nature of the process was not evident. Not long thereafter Case 2, while being examined because of an unrelated complaint, gave a history of total ophthalmoplegia a few years previously, and the hospital file provided the excellent account of the illness presented above. In Case 1 the course of the illness was followed more closely, and the association of mild weakness of the upper limbs, objective sensory changes, a facial palsy and particularly the high cerebrospinal-fluid protein provided good evidence that the syndrome was related to the Guillain–Barré type of polyneuropathy.

Table 1. *Summary of Cases.*

Case No.	Age	Period of Development	External Ophthalmoplegia	Pupillary Reaction to Light	Ptosis	Bell's Phenomenon	Fundi	Facial Weakness	Ataxia	Weakness of Limbs	Paresthesias
	yr.	*days*									
1	45	4	Total	Sluggish	Moderate	Absent	Normal	? (late)	Severe	?	Present
2	63	2	Total	Sluggish	Retraction of lids	Absent	Normal	Absent	Severe	Absent	Absent
3	63	5-6	? Gaze downward preserved	Sluggish	Moderate	Present	Normal	Absent	Severe	Absent	Slight

*Not examined.
†Normal at 6 wk.

In all 3 cases a respiratory complaint (severe in 2 and mild in 1) preceded the onset of neurologic complaints. In order of appearance, the symptoms in the 3 cases were as follows: Case 1, sore throat, "dizziness," tightness in the chest, unsteadiness, "drunken" gait, malaise, horizontal diplopia, numbness of fingers, soreness of arms and a splitting headache on coughing; Case 2, pneumonitis, fever, drowsiness, ataxia of the hands, burning and tearing of the eyes, frosting of vision, inability to read and severe ataxia of gait; and Case 3, pneumonitis, fever, severe bilateral frontal headache, diplopia on distant vision, pins-and-needles sensation in the fingers and an ataxic gait. In each case the full-blown clinical picture had developed over a period of three or four days.

At the height of the illness, external ophthalmoplegia was complete in 2 cases whereas in the third (Case 3) downward gaze was still present (however, this was reported verbally to have been absent the day before). The eyes were properly aligned and fixed in the central position. In 2 cases Bell's phenomenon was absent. Quick rotation of the head produced no ocular movements. Ice-water vestibular stimulation was not employed. The pupils were equal and moderately dilated, and reacted very sluggishly, but definitely, to light. Ptosis was moderate in 2 cases whereas in Case 2 the lids appeared retracted. The orbicularis oculi contracted strongly in all 3 cases. The visual acuity, visual fields and fundi were not remarkable.

Ataxia was a striking finding. In 2 cases it was of such severity that walking was scarcely possible and the patient could not feed himself. In Case 3 incoordination of the hands was of only moderate degree, but the gait was reeling and broad-based. In 2 cases there were no sensory changes in the limbs to account for the ataxia. In Case 1, although vibration sense was impaired, position sense was normal, and the Romberg test was negative. The ataxia in each case involved the upper and lower limbs, and in at least 2 cases co-ordination was not influenced by closure of the eyes. Stance and gait were severely affected. Nystagmus, of course, was not present while the eyes were immobile, but even during the period of recovery, it was not prominent and was noted only in Case 1.

Mental changes did not take place, but in Case 2 mild drowsiness occurred at the onset. This relative lack of psychologic disturbance was of importance in that the combination of ocular palsy and ataxia suggested Wernicke's disease, in which mental aberration, confusion and stupor are prominent findings. In 2 cases headache aggravated on coughing was present in the early phase of the illness. In no case was the face numb. The bulbar musculature was spared, except for weakness on chewing in Case 1. The bladder and bowel were not affected.

Outstanding in the course of the illness was the tendency for the patient to recover almost completely,

TABLE 1 *(Concluded).*

CASE NO.	SENSORY DEFICIT	TENDON REFLEXES	HEADACHE	DROWSINESS	MENTAL CHANGE	DIPLOPIA	FEVER	RECOVERY	DURATION OF DISEASE	CEREBROSPINAL-FLUID PROTEIN	THERAPY
									wk.	*mg./100 ml.*	
1	Present	Absent	Present	Absent	Absent	Present	Absent	Good	12	348	None
2	Absent	Absent	Absent	Mild	Absent	Absent	Absent	Complete	7	—*	None
3	Absent	Absent	Present	Absent	Absent	Present	Absent	Good, except for mild diplopia	12	—†	Sporadic

*Not examined.
†Normal at 6 wk.

Evidence of a peripheral neuropathy was scanty except in Case 1. Case 2 at no time showed motor or sensory involvement of the limbs or face. Case 3 had fleeting numbness of the fingers, but no weakness or objective sensory alteration was found. However, in both these cases the tendon reflexes disappeared at the height of the illness and returned during convalescence. Case 1 clearly portrayed more widespread involvement. The fingers were transiently numb, and for several days sensation for vibration and pain was impaired. The jaw tired when the patient chewed meat, the voice became hoarse after much talking, the shoulder muscles felt weak, and the arms were lame or sore. Furthermore, during recovery a complete left-sided peripheral facial palsy, which may have been part of the original illness, appeared. However, except for the facial palsy, these signs were not striking and cleared so promptly that disagreement arose concerning their significance before the nature of the illness was more firmly established by the finding of a raised protein level in the cerebrospinal fluid. In addition, these signs of peripheral nerve involvement in Case 3 were so completely eclipsed by the ocular and ataxic manifestations that they might well have been overlooked if they had not been carefully searched for. The tendon reflexes had disappeared, but the patient thought that his reflexes had always been difficult to elicit.

improvement beginning only a few days after the neurologic deficit had reached its height. Headache, paresthesias and malaise cleared within a day or two. In Case 1 sensation was restored to normal by the thirteenth day. Ataxia rapidly diminished and disappeared completely between the twenty-fourth and the thirty-fifth day of illness. The tendon reflexes were found to have returned by the fourth week in Cases 2 and 3, but in Case 1 they were still absent at three months.

Ocular movements began to appear a few days after the height of the illness and were approaching complete restoration in eight to twelve weeks. In Case 1 the changes could be closely followed; conjugate downward gaze was regained first, about the thirteenth day of illness. Convergence returned soon after. Conjugate lateral movements first appeared at about two weeks, and made their greatest gain around the end of the fourth week. Improvement occurred gradually thereafter, and at three months near vision was perfect, but diplopia occurred on distant vision when the eyes were fatigued. Vertical gaze had not appeared by the twenty-fourth day but was evident at the end of six weeks. The symmetry with which ocular motion recovered in the two eyes was most striking, and this feature is discussed below.

The pupillary reaction to light became brisk again within a day or two of the time at which the ocular paralysis had become complete. Ptosis had disappeared by the thirteenth day.

The remarkable recovery in all cases took place

without any special therapy. In Case 1 thiamine was first used after improvement had already been noted, and the return of function seemed not to be speeded. In Case 2 no therapy was directed toward the neurologic complaint. In Case 3 neostigmine and vitamin B_{12} had no observable effect.

Laboratory studies were for the most part within normal limits. The urine, blood and roentgenograms of the skull were not remarkable. The sedimentation rate in Case 1 was only 4 mm. in one hour. The cerebrospinal fluid was initially normal in Case 1, but at the end of four weeks the protein had risen from 36 to 348 mg. per 100 ml., the cell count remaining low. In Case 2 the fluid was not examined, and in Case 3 there was no abnormality even after a period of six weeks. The blood and cerebrospinal-fluid Wassermann test was negative. The electroencephalogram was normal or nearly so.

Fever, when present as a prodromal sign, abated promptly once the syndrome became fully developed. The blood pressure was raised in 2 cases but normal in the other. The presence of hypertension and ocular palsies coupled with the age of 2 of the patients (sixty-three) led to the diagnosis of cerebrovascular disease involving the brain stem. In Case 2 there had been an episode of myocardial infarction a few years previously. Two patients (Cases 2 and 3) were being treated in a hospital for acute chest disease, probably a pneumonitis, when neurologic complications developed, and a "toxic" effect of penicillin and streptomycin was suspected at the time as a causal factor. However, in Case 1 there had been no preceding antimicrobial therapy, although some respiratory distress ("like a cold") had occurred prodromally. Dietary insufficiency could not be regarded as an etiologic factor.

Discussion

Review of the Literature

Acute bilateral ophthalmoplegia of the degree exhibited by these 3 patients is an uncommon event and has been reported chiefly in acute idiopathic polyneuritis in association with severe widespread paralysis. (Pinckney,[1] in 1936, described 2 cases, Garvey and Slavin,[2] in 1938, 1 case, Baker,[3] in 1943, 1 case, Dempsey et al.,[4] in 1947, 1 case, and Haymaker and Kernohan,[5] in 1949, 1 case.) Correct diagnosis under these circumstances should not be difficult. It is a different matter when involvement is restricted largely to the ocular musculature, and the literature contains only one reference to such an occurrence. Collier,[6] in 1932, recognized two types of epidemic polyneuritis: the type described by Holmes and by Bradford, Bashford and Wilson in which there was a four-limb peripheral neuritis and facial diplegia (this is probably the Guillain–Barré type); and a four-limb peripheral neuritis associated with an external ophthalmoplegia. The latter was described as apyrexial, painless and rapidly appearing. In some the eye muscles were severely affected, and the limbs only mildly, perhaps with some extensor weakness and "jerklessness." The external ocular muscles could be completely paralyzed, but the internal muscles usually escaped. The ophthalmoplegia was of the "nuclear" type, affecting both eyes, but could be asymmetrical. The cerebrospinal fluid showed no definite changes. Recovery was rapid and complete. Collier[6] said that if the two types were related, overlapping might be expected, but he had not seen such a case. He related that in a period of a few weeks he had occasion to see 5 cases of irregular bilateral ophthalmoplegia of rapid onset with no general illness. All patients made a progressive and complete recovery. One died two months later of bronchopneumonia, and pathological examination showed nothing abnormal. These cases were to be reported in detail at a later date, but no reference to the paper could be found.

There can be little doubt that Collier[6] was referring to the same type of case as those reported above. However, he did not enter into any more complete description of the illness than that just quoted, and apparently the occurrence of ataxia was not noted. The relation of the two types that he described can probably be regarded as established by the findings in Case 1 presented above.

The only additional reference to the condition under discussion was by Mastrangelo[7] (1939), who described the case of a man of fifty-eight in whom paralysis of all the external muscles of both eyes, marked ptosis, supraorbital headache, tenderness of both eyes, weakness of the lower limbs and changes in tactile sense developed within a few days. However, a stimulus to the cornea provoked elevation of the eyes. All symptoms disappeared within a few months. The author suggested that the lesion was "toxi-infectious" and was located in the posterior white commissure and the posterior longitudinal bundles. His patient was addicted to alcohol and tobacco.

Differential Diagnosis

If the 3 cases presented above are representative of the clinical picture, it can be safely stated that no other entity closely resembles the syndrome. *Vascular disease* (hemorrhage or infarction) involving the brain stem is most unlikely to produce extensive ophthalmoplegia and ataxia without also damaging the reticular formation and thereby profoundly affecting consciousness. Thrombosis of the basilar artery is likely to cause ocular palsies, but the long motor and sensory tracts are nearly always involved too. In basilar-artery occlusion symptoms and signs can develop over a period of three or four days, but in stepwise, stuttering fashion rather than gradually and smoothly as in these cases. Nonetheless, vascular disease of some type was suspected in each case, and

this had a practical aspect since in 2 the question of anticoagulant therapy was raised.

Wernicke's[8] encephalopathy probably bears the greatest similarity to the present syndrome. Wernicke's original patients exhibited ataxia and ophthalmoplegia, but in addition consciousness was clouded — a feature that is usually considered a cardinal characteristic of Wernicke's syndrome. He noted that the ophthalmoplegia could be total except for the levator palpebrae and the pupil. However, total external ophthalmoplegia is the exception and occurs in only the most advanced stages of the disease. For example, in 52 cases of Wernicke's encephalopathy developing in a Singapore prisoner-of-war camp, complete external ophthalmoplegia was encountered only once and that terminally in a fatal case.[9] A peripheral neuropathy often accompanies Wernicke's encephalopathy, and in this respect there is again a similarity to the present syndrome. On the other hand, Wernicke's disease is closely related to malnutrition (vitamin B_1 deficiency), and this was not a factor in the present cases.

Tumors of the brain stem or the base of the skull would be most unlikely to mimic the syndrome. Pituitary apoplexy bears only a most superficial resemblance. Botulism and acute myasthenia gravis must be kept in mind.

Possible Relation to Acute Idiopathic or Infective Polyneuritis

It has already been pointed out that the great rise of the spinal-fluid protein in Case 1 provided good evidence that in at least that case the illness most probably was acute idiopathic neuritis, especially in view of the weakness and sensory changes in the limbs. There certainly seems to be no need to postulate two separate diseases, one producing the main features of the syndrome, and the other the peripheral neuropathy. The loss of reflexes in the other 2 cases and the presence of paresthesias in 1 also pointed to peripheral nerve involvement. Furthermore, the fact that a similar type of ophthalmoplegia develops in some cases of widespread polyneuritis suggests that the syndrome under discussion is a special form of polyneuritis. Such a case was carefully followed by Dr. Charles S. Kubik, who has kindly allowed me to report the details below (the illness was characterized by total external ophthalmoplegia, complete facial palsy bilaterally, severe paralysis of the upper limbs and a lesser degree of paralysis of the lower):

In I.R. (M.G.H. 702370), a 49-year-old woman, the following signs developed in order over a period of 6 days: diplopia; complete inability to open the left eye; inability to close the right eye; staggering gait; left-sided facial weakness; weakness of both upper limbs; aching across the shoulders; thick speech; nausea; vomiting; and slight numbness under the nail of the left middle finger. On admission, examination showed almost complete bilateral ptosis. There was complete external ophthalmoplegia on the left and paralysis of all movements except adduction and downward movement of the right eye. The pupils were equal and reacted to light. The masseters were extremely weak, and facial paralysis was nearly total bilaterally. The upper limbs were immobile, and the lower limbs could scarcely be lifted from the bed. The tendon reflexes were absent in the arms, but the knee and ankle jerks were brisk. Sensation was intact.

During the next 2 days all signs worsened. Dr. David G. Cogan found that the external ophthalmoplegia had become complete, but a fairly good Bell's phenomenon was obtained. Although ptosis was marked the lids retracted well on upward gaze. Irrigation of the left ear with cold water produced vertigo and nausea but no deviation of the eyes.

On the 11th day of the illness improvement began; the eyelids elevated better, and flexion of the elbows was a little stronger. On the 34th day conjugate gaze was 5-10° upward, 45° downward and 0 for the abducting eye and 10-15° for the adducting eye laterally. The symmetry of recovery of function of the 2 eyes was striking. On the 87th day the extraocular movements seemed normal objectively. Weakness of the facial musculature and of the limbs was still marked, but remarkable improvement occurred in the next year. The patient definitely had diplopia for 6 months, but after that ocular movements were subjectively normal. The spinal fluid on the 10th day of illness was crystal clear and had a protein of 54 mg. per 100 ml.; on the 2d day of the illness the value had been 14 mg. A diagnosis of infective polyneuritis or Guillain–Barré syndrome was made.

In this case, the ocular signs were not much different from those in the present group of cases, and the association of severe facial and limb paralysis of the peripheral type leaves little doubt of the correctness of the diagnosis. Ataxia was present on the second day of illness but was not detected on admission, although tested for at a time when the lower limbs still retained fair power. It is to be noted that the tendon reflexes in the lower limbs could still be elicited when weakness was already widespread.

Another illustration of the same association is provided by the following case, in which a widespread peripheral neuropathy was associated with greatly impaired ocular movements (the patient died later and neuropathological examination showed the changes of acute idiopathic polyneuritis):

The patient (M.G.H. 647543), a 24-year-old woman, over a period of 18 hours, noted a severe paralysis of the face, arms, trunk and legs. Shortly thereafter breathing became embarrassed, pooling of the oral secretion in the pharynx began, and diplopia appeared. Examination of the eyes 48 hours after the onset showed marked ptosis bilaterally. Both eyes were elevated at rest and could not be depressed to the central position. Adduction and abduction of the right eye were fairly good, but much restricted on the left. The pupils were equal and reacted to light. Eye movements began to improve within a few days, but recovery of respiratory function was poor and the patient died on the 43d day of illness. Neuropathological examination (by Dr. Raymond D. Adams) showed a severe destruction of myelin in many of the peripheral nerves associated with a brisk perivascular mononuclear infiltration. No abnormality was seen in the brain stem, including the oculomotor nuclei. (Eye movements had been restored to normal at the time of death.)

All in all, it seems justifiable to regard the syndrome under discussion as closely allied to or part of acute idiopathic polyneuritis.

Interpretation of Some of the Clinical Features

Ophthalmoplegia. The remarkable symmetry of

the external ophthalmoplegia, particularly during the period of recovery (in Case 1), hardly suggests peripheral involvement of the separate oculomotor nerves bilaterally. It will be recalled that in the early period of recovery, conjugate gaze downward and convergence had both become almost normal again when conjugate lateral and upward gaze were still severely limited. At later stages the recovery of conjugate lateral gaze was always almost exactly symmetrical — something not to be anticipated in lesions of peripheral nerves. Also, the existence of a total external ophthalmoplegia, with relative sparing of the levator palpebrae and the pupillary reaction to light, points to a more centrally placed interruption. Furthermore, the perfect alignment of the eyes during the period of complete immobility has usually been interpreted as indicative of a supranuclear lesion. Duke-Elder[10] has the following explanation:

> . . . only in the rare event of a widespread lesion in the upper brain stem isolating the motor nuclei completely from all down coming excitations and inhibitions and yet completely sparing them does complete bilateral external ophthalmoplegia with the abolition of all movement result from supranuclear disturbance: such lesions are distinguished by their characteristics of retracted lids [as in Case 2 of the present report], the maintenance of parallelism of the eyes, and the absence of diplopia from nuclear lesions which show an irregularity in the incidence of ptosis, a loss of parallelism and diplopia.

It cannot be disputed that the occurrence of diplopia and some degree of ptosis in each case points to peripheral involvement of the oculomotor nerves. Therefore, one is forced to conclude either that there is both a peripheral and a central affection of the oculomotor apparatus or that peripheral lesions can be so remarkably symmetrical in this syndrome that paralyses of conjugate gaze are closely simulated and so selective that the levator palpebrae and the pupil may be spared. The most thorough pathological studies in cases of infective polyneuritis fail to demonstrate any changes within the neuraxis, and there is thus no morbid anatomic basis for attributing the clinical picture to a disturbance within the brain stem. Since, in infective polyneuritis with lesser involvement of the ocular system, the clinical findings point to peripheral lesions, it is not unlikely that in the present cases the pathologic process was located in the peripheral part of the oculomotor nerves and merely displayed an unusual symmetry. However, further observations are necessary to establish this point.

Ataxia. In each case inco-ordination was a striking feature and in its rhythmical jerky character seemed clearly to be of a cerebellar type. However, in view of the lack of pathologic changes within the cerebellar system in cases of infective polyneuritis and a certain reluctance to upset well established ideas concerning the disease, this impression has had to be re-examined. Ataxia has been frequently described in the Guillain–Barré syndrome but usually was attributable to easily detected sensory changes in the limbs. In the cases reported above, the situation was quite different. In Cases 2 and 3 no objective sensory deficit at all could be found at a time when both patients displayed an extremely ataxic gait, and indeed 1 could not feed himself. There was no motor weakness. In Case 1 sensory changes were present, vibration sense in particular being impaired, but the ataxia appeared to be out of all proportion to the sensory loss. Here, again, the conclusion is unavoidable either that the inco-ordination was in fact cerebellar in origin or that a scarcely detectable or even undetectable disturbance of peripheral sensation can produce a profound motor ataxia. Certainly, in routine neurologic practice, I have not encountered such degrees of ataxia even with much more severe sensory loss. If the cerebellar system is not to be incriminated one must postulate that in the syndrome herein discussed, a unique, widespread and selective attack on the sensory neurons underlying postural adjustments must have occurred. It might be pointed out that in none of the cases was "cerebellar speech" encountered.

To theorize for a moment, if the ophthalmoplegia and the ataxia could be traced to involvement of the central nervous system, the evidence would point to a disturbance of the specific systems subserving conjugate gaze and co-ordination of limbs respectively. In this respect there would be some resemblance to Wernicke's encephalopathy, the hallmarks of which are ophthalmoplegia, ataxia and mental alteration. However, as already stated, although there is good similarity in some of the ocular signs, the minds of the patients described above were clear for the most part, and, furthermore, ataxia has been a variable feature in Wernicke's syndrome, being found in only 4 per cent of cases developing as the result of malnutrition in Japanese prison camps.

Areflexia. In Cases 2 and 3 the temporary loss of all tendon reflexes, with little or no sensory disturbance, was a surprising feature. In Case 1 the tendon jerks were also in abeyance when the sensory deficit was mild and motor power almost normal, but they had not reappeared at the end of three months. Judging from Cases 2 and 3, one would have to postulate a very selective involvement of special sensory neurons subserving the stretch reflexes or conclude that the reflex mechanism is a sensitive and easily deranged one, defaulting when all other evidences of acute neural insult are lacking.

Summary and Conclusions

Three cases characterized particularly by total external ophthalmoplegia, ataxia and loss of tendon reflexes are presented. The nature of the illness was not recognized until the third case was seen, when, in association with a mild peripheral neuropathy, the cerebrospinal fluid showed an albuminocytologic dissociation and the total protein rose to 348 mg. per

100 ml. Thus, the syndrome proved to be a variant of acute idiopathic polyneuritis (the Guillain–Barré type of polyneuropathy) in which limb involvement was minimal or absent. Vascular disease of the brain stem was suspected in each case.

The clinical picture is apt to be alarming unless the existence of such an illness is appreciated. The clinical course is favorable, and relatively complete recovery is the rule. Several features of the syndrome, particularly the ophthalmoplegia and the ataxia, point to an involvement of the central nervous system, but in view of the well established pathologic changes in cases of infective polyneuritis (Guillain–Barré syndrome), the clinical signs in question are reluctantly interpreted as manifestations of an unusual and unique disturbance of peripheral neurons. Especially does it seem that the ataxia was cerebellar in type.

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WHICH NODULAR GOITERS SHOULD BE REMOVED?*

A Physiologic Plan for the Diagnosis and Treatment of Nodular Goiter

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WHEN the clinician discovers a nontoxic nodular goiter, he is often confronted with the decision whether it is necessary to remove the thyroid nodule. One group of authors cites a high incidence of thyroid cancer in nodular goiter and advises immediate surgical removal.[1-3] Contrariwise, another group states that thyroid cancer is quite rare, even in nodular goiter, and advises either medical or no therapy in the majority of such patients.[4-6] Much of the controversy over the management of nontoxic nodular goiter stems from this conflict concerning the incidence of thyroid cancer.

It is the purpose of this report to review the facts on which these divergent views are based. In so doing, it attempts to answer the following questions:

What is the frequency of nontoxic nodular goiter in an unselected population?

What is the frequency of cancer in the nodular goiter of such an unselected population, and does it differ significantly from the frequency of cancer in surgically removed nodular goiters? Is the incidence of thyroid cancer significantly higher in uninodular than in multinodular goiter?

How accurately can the clinician differentiate the uninodular and the multinodular goiter?

Do benign thyroid nodules become malignant? Is prophylactic surgery justified?

Is it possible to differentiate benign and possibly malignant thyroid nodules before operation?

Can apparently benign nodular goiter be safely and effectively treated by medical rather than by surgical means?

Having reviewed the pertinent literature and presented our experimental and clinical data, we shall outline a diagnostic and therapeutic regimen that we have found useful.

Frequency of Nontoxic Nodular Goiter in an "Unselected" Population

Two types of studies appear to give a relatively unselected population from which the incidence of nodular goiter can be obtained. The first method is clinical: a large series of normal subjects or patients who have no thyroid complaints are carefully examined for nodular goiters. The second method is the pathological: the thyroid glands from consecutively autopsied bodies are carefully sectioned and examined. Many of the nodules found by the pathologist undoubtedly would be too small to be palpated by the clinician. Therefore, the data in the literature have been carefully evaluated so that the incidence of potentially palpable nodules (1 cm. in diameter or larger) in the autopsy studies can be compared with that of nodules actually palpated in the clinical

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studies. Schlesinger et al.[7] have arbitrarily selected nodules of 1 cm. in diameter as the ones that should be palpable; most authors since then have accepted this criterion.

Vander and his associates,[8] in Massachusetts, examined over 5000 apparently normal adults between the ages of thirty and fifty-nine years. As noted in Table 1, 4 per cent had palpably nodular goiters. Three quarters of these were considered clinically to be solitary nodular goiters. In the endemic goiter

TABLE 1. *Incidence of Palpated Nodular Goiter in Clinical Studies of Unselected Population.*

Source of Data	Sex	Age	Solitary Nodules	Multiple Nodules	Total Nodules
		yr.	%	%	%
Vander et al.[8]	Males & females	30-59	3.0	1	4.0
Miller[9]	Females	>20	—	—	11.0
	Males & females	>20	—	—	8.0*
Crile & Dempsey[10]	—	—	1.0	3.0	4.0
Slater[11]	Males & females	>20	2.2	1.3	3.5
		30-59	2.5	1.5	4.0

*Calculated.

area of Detroit, Miller[9] reported that 11.2 per cent of the female adult hospital and clinic population had asymptomatic nodular goiters. Since nodular goiter is more common in women, he calculated that the incidence for both sexes would approximate 8 per cent in this area. Crile and Dempsey[10] reported that 4 per cent of patients admitted to the hospital in Cleveland for diseases other than that of thyroid origin had nodular goiter. In a series of approximately 1000 persons without thyroid complaints, one of us[11] palpated nodular goiters in 4 per cent of the adult patients of both sexes between the ages of thirty and fifty-nine. Approximately 60 per cent of these incidentally discovered nodules were solitary. Thus, approximately 4 to 8 per cent of adults appear to have nontoxic nodular goiters, and in the nonendemic areas, about two thirds are clinically solitary nodules.

Although it is more difficult to obtain comparable data from published studies of autopsy cases, an analysis of the literature gives the calculated incidence of nodular goiter in unselected adults who were autopsied (Table 2). Hellwig[12] reports that 51 per cent of his subjects had thyroid nodules. However, only 14 per cent of these patients, or 7 per cent of the total series, had nodules that were 1 cm. or more in size. Thus, 7 per cent of his series had potentially palpable thyroid nodules. Schlesinger and his co-workers[7] report that 8 per cent of their autopsied series had thyroid nodules that were at least 1 cm. in diameter. Hull's[13] data indicate that 12 per cent of his subjects had potentially palpable thyroid nodules. Of these, 7 per cent would have been clinically considered uninodular and 5 per cent multinodular. Thus, the incidence of potentially palpable nodular goiter is calculated to be between 7 and 12 per cent. This figure is about one and a half times that actually reported by clinicians (Table 1).

The incidence of nodules of all sizes found at autopsy is considerably greater than that of potentially palpable nodules; about 50 per cent of all autopsied glands have more than one nodule, and 12 per cent have single nodules. Only about 20 per cent of all single nodules found at routine autopsy examination are large enough to be potentially palpable by the clinician.

Frequency of Cancer in Nodular Goiter of an Unselected Population and in Surgically Removed Goiters and Comparative Incidence of Thyroid Cancer in Uninodular and Multinodular Goiters

None of the 35 patients in the series of Vander et al.[8] who had thyroidectomy had cancer of the thyroid gland. Most of these patients had uninodular goiters. From Miller's data, one cannot compute the incidence of cancer in the asymptomatic goiters. In Slater's[11] group of patients 13 have had thyroidectomies; of these, 1 case was diagnosed as cancer by the pathologist.

TABLE 2. *Incidence of Potentially Palpable Nodular Goiter in Autopsied Series of Unselected Population.*

Source of Data	State	Age	Clinically Uninodular Goiters	Clinically Multinodular Goiters	Total Nodular Goiters
			%	%	%
Hellwig[12]	Kansas	Adults	—	—	7
Schlesinger et al.[7]	Massachusetts	Adults	—	—	8
Hull[13]	Colorado	Adults*	7	5	12

*30-59 yr. of age.

Sokal[14] reviewed the reported data of 100,000 routine autopsies and found an incidence of 0.1 per cent of thyroid cancer; the incidence in these component reports varied from 0-0.2 per cent. These reports were mainly retrospective—that is, the data were culled from autopsies routinely performed in the past, with no particular attention to the thyroid gland. Furthermore, the reports represent the incidence in subjects with and without thyroid nodules. In a series of 221 autopsies[13] in which the thyroid glands were carefully studied as the autopsies were performed, 3 incidental and unexpected cases of cancer were found in what clinically would have been considered uninodular goiters. From the data presented, and assuming 1 cm. to be the minimal size of a nodule that can be palpated, it can be calculated that cancer would have been found in about 5 per cent of the clinically

nodular goiters in this series and in 9 per cent of clinically uninodular goiters. However, it should be emphasized that the cancers were incidental findings in septuagenarians who died of other causes. In this series, no cancer was found in any of the nodular goiters present in patients under seventy years of age. On the other hand, patients with previous thyroidectomies had been eliminated from the study, and it is possible that some patients with clinically significant cancer were thus excluded. In the series of Hazard and Kaufman[15] about 1.5 per cent of the pathologically nodular glands contained incidental cancer, but no estimate can be made of the incidence of cancer in nodules that were large enough to have been palpable.

It is apparent that insufficient data are available to justify a reasonable conjecture about the incidence of cancer in nodular goiter in the unselected population. The meager clinical data suggest an incidence of about 2 per cent whereas the autopsy data, where figures can be derived for the incidence of potentially palpable nodules, suggest an over-all figure of 5 per cent.

More exact information is available for surgically removed thyroid glands. The incidence of carcinoma in excised nontoxic nodular goiter varies from 3.7 to 18 per cent, with the values uniformly distributed between these limits. In the nontoxic *multinodular* glands, the incidence of carcinoma was reported as only 0.6 per cent by the Lahey Clinic,[16] but 6 other authors[1,17-21] report an incidence of between 3.4 and 10.4 per cent. Of 11 reports on cancer in clinically uninodular glands, only 1[19] mentions an incidence of less than 9 per cent whereas 8[12,17,18,20-23] of the remaining 10[16,24] state that 14 to 33 per cent of their patients with uninodular goiters had cancer. Thus, cancer in surgically removed glands is more frequent in uninodular than in multinodular goiter.

The frequency of carcinoma in these surgical series is higher than would be expected from the data derived from unselected populations. In many of the reports, an attempt has been made to reduce somewhat the element of selection by eliminating from the series patients with clinically obvious cancer. After the cases considered to be cancer preoperatively are excluded the incidence in the benign-appearing nontoxic nodular goiter is in the range of 3.7 to 7.6 per cent, with a single report of 11.5 per cent. The autopsy data from Hull's[13] study can be calculated in a similar manner; the findings are similar to those mentioned above.

When further statistics concerning the frequency of cancer in the thyroid nodules of an unselected population are available, they will probably indicate a figure lower than that found in the surgical series. In fact, Dailey et al.[25] report cancer in 0.2 per cent of their autopsied series as compared to 4.8 per cent in their surgical series of nontoxic nodular goiter. This is probably due to the fact that the patients operated on constitute a select group and that the autopsy study was a retrospective one. Those who undergo surgery are usually the patients who have hoarseness or in whom their physicians have noted that the nodules are hard or enlarging. The important question, which at present cannot be definitively answered, is how much difference exists between the frequency of cancer in an unselected group of asymptomatic thyroid nodules and in a group selected for surgery. However, our analysis of the literature does indicate that the incidence of cancer in the unselected uninodular and multinodular goiter may be 2 to 5 per cent whereas in the surgically treated multinodular goiter it is between 3 and 10 per cent, and in the surgically treated uninodular goiter, it is between 9 and 33 per cent.

Accuracy of Clinical Differentiation of Uninodular and Multinodular Goiter

As pointed out above, there is almost unanimous agreement that cancer is more frequent in the uninodular than in the multinodular goiter. Most authors stress the fact that the uninodular goiter is especially likely to be malignant and should be removed. Thus, clinical differentiation of uninodular and multinodular goiter seems advisable.

The clinician will often err in his clinical appraisal of the physical state of the thyroid gland. Normally, there may be some asymmetry of the gland. Even as experienced an observer as Lahey[26] has reported that at times he was unable to decide whether the gland that he was palpating was normal or nodular. In elderly patients in particular, the thyroid gland seems to have dipped into the thoracic inlet so that it can barely be palpated; often, only the top of the gland can be felt. Thus, the clinician cannot determine the degree of nodularity of these glands. Even when the gland seems satisfactorily situated for thorough palpation, the attempt to differentiate uninodularity from multinodularity of a goiter is fruitless in about a third of the cases. In fact Beahrs et al.[27] report that they no longer attempt such a differentiation.

On the other hand, despite the realization that clinical judgment may be fallacious, Cope and his associates[2] conclude that it is clinically important to attempt this differentiation. They report that cancer was twice as frequent in the clinically solitary nodular goiter, or in the goiter restricted to one lobe (even though multinodular), as in the bilaterally multinodular goiter. Similarly, Ravdin[28] states that, despite the errors in clinical differentiation, it seems mandatory that clinically isolated thyroid nodules be removed. We agree that clinical differentiation between uninodular and multinodular goiter should be attempted. (There seems to be less danger of cancer in the multinodular gland.)

Possibility of Malignant Change and Advisability of Prophylactic Surgery

Since thyroid cancer is relatively rare and nontoxic nodular goiter is very common (especially in elderly patients), it is important to know whether benign nodules can become malignant. If malignant degeneration of benign thyroid nodules does occur, the prophylactic removal of thyroid nodules would be advisable to prevent the development of cancer. Contrariwise, if this change from benign to malignant tumor is most infrequent, prophylactic surgery is unnecessary.

In 1883, Wölfler[29] stated that fetal rests may become tumors in adult life; he believed that benign tumors did become malignant. Wegelin[30] pointed out that thyroid tumors are the end result of previously prolonged hyperplasia. Marine[31] observed the development of hyperplasia and ultimately of nodular goiter in the thyroid glands of patients with iodine deficiency. Antithyroid drugs and other goitrogens similarly cause hyperplasia and multinodular goiters. After a careful review of the physiologic factors controlling hyperplasia, Rawson and Rall[32] concluded that prolonged excessive stimulation may cause experimental thyroid cancer in animals.

The evidence and opinions of most authors are against the development of human cancer from a pre-existing benign nodule, whether it is of the hyperplastic, adenomatous variety or a true adenoma. If benign tumors did become malignant, there should be more benign and less malignant tumors in youth, with a gradual increase in the ratio of malignant to benign lesions with increasing age. The findings in all autopsied series stress the rarity of benign tumors in subjects less than thirty years of age. On the other hand, the incidence of thyroid cancer in surgical series of thyroidectomies in youth for nodular goiter ranges from 31 to 59 per cent[33]; this is distinctly higher than the range reported for adults. Sloan[3] indicates that the nontumorous portion of the gland in most patients with thyroid cancer is normal and not adenomatous. He also states that cancer is no more frequent in patients with multinodular goiter than in those without adenomatous goiter. He concludes that nodular goiter rarely precedes cancer. Crile[18] reports that 80 per cent of thyroid cancers arise without known preceding goiter. If a hyperplastic nodule were a premalignant lesion, thyroid cancer should be much more frequent in multinodular goiter (with its many foci) than in a uninodular goiter. The data reported above refute this possibility. Meissner and McManus[34] report that most benign tumors are follicular and cancerous tumors are papillary. Sloan,[35] Cope et al.,[2] Crile and Dempsey[10] and Meissner and McManus[34] all conclude, then, that cancerous thyroid nodules were malignant from the start and not transformed from a benign nodule. Thus, the indication for surgical removal of nodular goiter should be aimed at diagnosis and removal of existing cancer and not at preventing the development of future cancer.

The number of nontoxic nodular goiters that would have to be removed for this prophylactic purpose would exceed 1,000,000 in this country. The morbidity and mortality from such widespread surgery would greatly exceed the present morbidity and mortality from thyroid cancer. Thus, it is more desirable to remove nodules that are most apt to be malignant rather than all nodules, most of which are benign.

Preoperative Differentiation of Benign and Possibly Malignant Nodules

In 1940, Hamilton, Soley and Eichorn,[36] using radioautographic studies of thyroid tissue slices, found that cancerous tissue retained practically no radioactive iodine whereas the normal pericancerous tissue concentrated large amounts of this isotope. Cope, Rawson and McArthur[37] and Rawson et al.,[38] using similar technics, reported that some benign hyperplastic nodules concentrated more radioactive iodine than normal tissue. Rawson and his associates[38] and Dobyns and Maloof[39] found that the maximum uptake of any of the cancerous nodules was decidedly less than that of normal thyroid tissue of the same patient.

In 1949, Dobyns, Skanse and Maloof[40] assayed, by means of a directional Geiger counter, the in vivo concentration of radioactive iodine over various parts of thyroid glands containing nodules. After these studies were made, thyroidectomy was performed. The in vivo studies corroborated the in vitro findings mentioned above. Means,[41] in 1950, stated, "so far we have never found a hot nodule which has shown histologic evidence of malignancy."

Using these reports as our guide, we compared the relative avidity of clinically solitary nodules or nodules limited to one lobe with that of the contralateral uninvolved part of the gland. A nodule was classified as "hot" if it collected considerably more isotope than the contralateral side and "cold" if it collected considerably less than the other side. Those with intermediate values were considered to be "warm" nodules. In 1954 Perlmutter et al.[42] reported that of 85 such solitary nodules, none of the 24 "hot" nodules were pathologically malignant, but 20 per cent of the "warm" and 32 per cent of the "cold" nodules were considered malignant by the surgical pathologist. Because we have been seeking a method of differentiating the benign from the possibly malignant nodules, we now classify the "warm" and "cold" nodules together. We now classify the nodules as either "hot" or "cold"; the latter group is considered to be possibly malignant. Table 3 presents the data that we have collected to date. With 1 exception, every hot

nodule in our series has been benign. The exception was a nodule, a lateral cervical lymph node, in a patient who had had a total thyroidectomy for proved thyroid cancer. The lymph node contained "lateral aberrant" thyroid tissue, which in fact is metastatic thyroid cancer. There was no other functioning thyroid tissue in this case. Johnson and Beierwalters[43] have performed similar studies using an automatic scintillation device; 31 per cent of their 32 patients with "cold" nodules had thyroid cancer, 10 per cent of the 10 with "warm" nodules had cancer, and neither of the 2 "hot" nodules was malignant.

Theoretical objections have been raised to ascribing the increase in radioactivity to a nodule when the nodular area has more radioactivity than the other side. It has been stated that a "cold" nodule may be surrounded by an area of normal thyroid tissue and give a false reading suggesting an active nodule. However, the reading might then be similar to, but it should not be greater than, the normal non-nodular other side. This may explain why some of the malignant nodules have been "warm." Since we now group the "warm" nodule with the "cold" nodule as possibly malignant, this objection is no longer valid. It should be emphasized that many cancer nodules are too small to be palpated. Thus, a minute cancer nodule may be missed in any thyroid gland — one that is clinically normal, diffusely enlarged or nodular. Therefore, although the finding that a palpable nodule is "hot" is strong evidence that this nodule is benign, it does not exclude the coexistence of a clinically impalpable cancer. To eradicate all these thyroid cancers, prophylactic, complete thyroidectomies would have to be performed on the entire population — obviously an impractical and undesirable procedure.

TABLE 3. *Correlation of the Isotopic and Pathological Nature of Solitary Nodules.*

Isotopic Description	Pathological Findings		Totals
	Benign Nodules	Malignant Nodules	
Cold	76	23	99
Hot	40	1*	41
Total			140

*Patient had previous total thyroidectomy for thyroid cancer; nodule tested was lymph node containing thyroid cancer.

Treatment of Apparently Benign Nodular Goiter

If the thesis that "hot" nodular goiter is benign is further corroborated, it would be safe to attempt medical therapy. "Hot" nodules that are producing excessive amounts of thyroid hormone, the so-called toxic adenomas, can be successfully treated with radioactive iodine. However, "hot" nodules that are nontoxic are not producing excessive amounts of hormone even though they are more active than the non-nodular tissue. If the functioning of the nontoxic, "hot" nodules is inhibited for a prolonged period, they may decrease in size. In 1940 Reinhoff[44] noted that the oral administration of thyroid caused decreases in the size of the simple colloid goiters. Greer,[45] in 1951, demonstrated that the ingestion of 0.06-0.2 gm. of thyroid (1-3 gr.) a day reduced the uptake of radioctive iodine by the thyroid gland to myxedematous levels. He concluded that the thyroid function was decreased by the ingested thyroid hormone. Perlmutter et al.[46] demonstrated that the ingested thyroid hormone did not decrease the gland's responsiveness to thyroid-stimulating hormone (TSH). They concluded that the pituitary body was inhibited by the ingested hormone and that the thyroid gland thus lacked pituitary stimulation. Prolonged loss of this TSH stimulation leads to atrophy of the thyroid gland, as noted in hypopituitarism. Perlmutter,[47] in 1953, reported a reduction in the size of the multinodular and of a "hot" uninodular goiter after the prolonged ingestion of thyroid hormone. Later in 1953, Greer and Astwood,[6] in a careful study of simple goiter, concluded that 87 per cent of 23 diffuse goiters decreased in size and 44 per cent underwent complete remission after the ingestion of thyroid; 67 per cent of their 18 single nodules responded, and 39 per cent disappeared after similar therapy. At the 1955 meetings of the American College of Physicians, Cope[48] reported that he had treated 150 patients who had goiters with thyroid ingestion; 25 per cent of the diffusely nodular goiters, 50 per cent of the small diffuse goiters and 50 per cent of postoperatively recurrent nodular goiters were greatly relieved by thyroid therapy. None of the very large adenomatous or single adenomatous nodules disappeared.

Thus, it seems that both the toxic and nontoxic "hot" nodular goiters are amenable to medical therapy.

Present Investigative and Therapeutic Regimen

When a patient with a nodular goiter is seen at the Endocrine Clinic of the Maimonides Hospital, his clinical status is carefully evaluated. In patients under twenty-five years of age and in those with clinical evidence of neoplasia, such as local lymph-node enlargement or fixation or hoarseness associated with vocal-cord paresis, surgical removal of the goiter is recommended regardless of the results of laboratory investigation. In the remaining patients, whose nodules are clinically benign, the following laboratory determinations are made, in decreasing order of frequency: the total twenty-four-hour uptake of I^{131}* by the thyroid gland; the level of serum protein-

*The radioactive iodine used in this study was supplied by the United States Atomic Energy Commission.

bound iodine; and the basal metabolic rate. In patients with uninodular goiters (and those with masses restricted to one lobe), directional counts are made over the various parts of the gland, and the uptake over the nodular area is compared with that over the presumably normal parts of the gland. By definition, a "hot" nodule is one that concentrates at least 125 per cent as much I^{131} as the non-nodular portion of the gland. A nodule that concentrates less than 125 per cent is considered "cold" (this includes the groups formerly called both "warm" and "cold"). In a multinodular gland with predominant nodules, directional counting is also done.

With these data, patients with clinically benign solitary nodules can be divided into various groups.

Total Uptake Less than 10 Per Cent

The most common cause for this low uptake in a patient with a nodule is the prior or concomitant administration of iodides or iodine-containing compounds. The patient may not be aware of the ingestion of iodides, for they may be contained in a cough mixture or vitamin-mineral capsules. Contrast mediums for x-ray visualization will usually contain iodine. Ingestion of thyroid hormone may also cause a diminished accumulation of I^{131} by the gland. In most cases, a repeated determination of the I^{131} uptake four to six weeks after cessation of the use of the interfering substance will give a valid result. The effect of certain iodinated dyes, however, such as those used for gallbladder visualization and for bronchography and myelography, lasts for many months.

If the low uptake in a patient with a nodular goiter is not due to an interfering medication, one must consider the possibility that the patient is suffering from subacute thyroiditis. It has been reported that there may be asymmetric enlargement of the thyroid gland in thyroiditis, resulting in the clinical impression of a nodule. We have seen 4 nodular goiters that on biopsy were proved to be thyroiditis. Three of the patients had uptakes of less than 10 per cent; the fourth had an uptake of 20 per cent, and the nodule was "hot" (this patient was in the subsiding stages of the disease). Therefore, in a patient with a nodule whose total I^{131} uptake is low (and in whom iodide ingestion can be reasonably excluded) and from whom a history of fever, sore throat, earache or tenderness of the nodule can be elicited, observation is considered indicated, and corticoid therapy may be given for amelioration of accompanying symptoms. In 2 cases so treated, the nodules completely disappeared in two or three months, with no surgical intervention. It is important to realize that subacute thyroiditis may present itself as an asymptomatic nodule.

Normal I^{131} Uptake

Euthyroid patients are classified as follows:

Those with "cold" nodules, who should have immediate surgical treatment of the nodule.

Euthyroid persons with a "hot" nodule, in whom the I^{131} uptake is repeated after the daily ingestion of 75 microgm. of tri-iodothyronine* for a week. This may be of value to predict effectiveness of thyroid therapy; 120 to 240 mg. of thyroid is ingested daily for at least three to six months. If the nodule disappears or decreases greatly in size with this therapy, no further treatment is recommended. If no change is noted, surgical removal is recommended at present. If future studies reveal that "hot" nodules are never malignant, surgery should be limited to removal of tumors causing local pressure symptoms.

Hyperthyroid patients. Some of the patients with a normal uptake and a "hot" nodule are hyperthyroid. Clinically, these cases are usually classified as "masked" hyperthyroidism rather than as examples of the classic picture of diffuse toxic goiter. The serum protein-bound iodine and basal metabolic rate are elevated. A positive result is obtained with a therapeutic trial of stable iodine or a thiouracil derivative. It is recommended that these patients have definitive therapy either with I^{131} or surgical removal.

High I^{131} Uptake

Euthyroid patients. A certain number of clinically euthyroid persons are seen who have a high uptake and a "hot" nodule whose serum protein-bound iodine is borderline low. Ingested thyroid hormone will cause a distinct suppression of the collection of I^{131} by the gland. A marked decrease in the size of the nodule usually occurs after a prolonged course of thyroid-hormone ingestion. It is postulated that the clinical and laboratory status of these patients is due to an iodine deficiency or to some defect in the synthesis of thyroid hormone by the thyroid gland. Thyroid-hormone therapy is the treatment of choice.

Hyperthyroid patients. In patients with a "hot" nodule usually occurs after a prolonged course of for the clinical state, and treatment with I^{131} or surgery is advised. Those with a "cold" nodule should be treated exactly as euthyroid persons with a "cold" nodule except that it is essential first to restore the patient to the euthyroid state before the recommended surgical procedure. In these persons the nodule is regarded as coincidental to the hyperthyroidism. Such cases have been cited in the literature, but we have seen none in our personal experience.

This discussion concerns uninodular goiter. Our experience with the use of I^{131} as a guide to therapy of multinodular goiters has been limited. When relatively discrete nodules can be evaluated for activity in

*Kindly supplied by Dr. A. Heming, of Smith, Kline and French Laboratories, Philadelphia.

a multinodular gland, it is believed that "coldness" may be considered an indication for surgical treatment. On the other hand, if the nodules are "hot," one may be inclined to observe the patient.

Summary and Conclusions

A review of the literature indicates that clinically palpable thyroid nodules are present in 4 to 12 per cent of the population of the United States. The incidence of cancer in unselected nodular goiters may be as high as 2 to 5 per cent. The incidence of cancer in surgically treated multinodular goiter is 3 to 10 per cent, and that in uninodular goiter 9 to 33 per cent.

Most evidence indicates that benign thyroid nodules rarely undergo malignant transformation, and therefore surgical therapy as a prophylaxis against carcinoma is not indicated. Excisional therapy is indicated for nodules that are considered likely to be carcinomatous.

A scheme for I^{131} evaluation of thyroid nodules for malignancy or benignancy is presented. Whereas 23 per cent of the physiologically hypoactive nodules have been found to be malignant, the hyperactive nodules are uniformly benign. These nodules may be successfully treated medically.

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ANEURYSM OF THE ABDOMINAL AORTA AND ILIAC ARTERIES*

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ANY artery in the body has the potential of dilating abnormally if weakness develops in the artery wall. If this dilatation is of significant degree, the lesion is described as an aneurysm. If the weakness and dilatation involves most of the circumference of the vessel, the aneurysm is described as fusiform; if one wall gives more than the others, a saccular aneurysm develops on that side. In either type, growth increases the bursting force on the wall as well as thinning the wall; consequently, rupture is a frequent and disastrous complication.

Aortic aneurysms have been recognized since the Middle Ages, and their dire prognosis has long stimulated interest in their therapy. In 1817 Sir Astley Cooper[1] ligated the aorta proximal to the aneurysm, with a fatal outcome. From then until the report of deTakats[2] in 1946 there were 30 operations of this type, with 6 survivals for more than a year. The first successful proximal ligation was performed by Matas[3] in 1923 for a ruptured syphilitic aneurysm of the aortic bifurcation in a twenty-eight-year-old woman. deTakats reported 2 more survivals of a year or more after proximal ligation.

While these attempts at control were being used, other methods were reported. In 1864 Moore inserted iron wire to reinforce or increase the clot along the walls of the aneurysms, thereby hoping to prevent rupture and to control pain. Wiring of abdominal aortic aneurysms has been performed in recent years with the use of stainless-steel wire[4] and in some cases with current passed through the wire to encourage thrombosis.[5] Results were not completely satisfactory owing to the occurrence of rupture despite wiring in some cases, and the occasional complete thrombosis of the aneurysm, with resultant distal ischemia.

The Matas endoaneurysmorrhaphy was successfully utilized to control a traumatic abdominal aneurysm by Bigger[6] in 1940, but the fusiform nature of arteriosclerotic aneurysms makes its consistent application impossible. Attempts have been made to reinforce the wall of the aneurysm from outside by use of cellophane but have not prevented rupture.[7]

Thus, no truly effective treatment of abdominal aortic aneurysm had been demonstrated up to the time of the first resection with arterial homograft replacement by Dubost et al.,[8] which was performed in 1951. Cooley, DeBakey and Creech[9] subsequently demonstrated the feasibility of this surgical approach in a large series of cases. The delay in arriving at this point is interesting in view of the fact that in 1907 Carrel[10] was successfully transplanting vessels in animals, for which he received the Nobel Prize in 1912.

The present discussion deals with our experience in treating 21 abdominal aneurysms by resection and replacement with homologous artery grafts.

ETIOLOGY

An increasing age and decreasing incidence of syphilis in the population of this country has caused arteriosclerotic abdominal aortic aneurysm to become the most commonly encountered major-vessel aneurysm. Of 13 patients in this series who had serologic tests for syphilis, only 2 were found to have positive tests. The pathological sections of the aneurysms in these 2 cases were consistent with an arteriosclerotic etiology, and it is difficult to demonstrate that syphilis played any part in their formation.

Hypertension might be thought to be a primary factor in the formation of arteriosclerotic aneurysms because of the unusual stress it would apply to a vessel weakened and dilated by arteriosclerosis. Hypertension is not essential in the production of aneurysm, however, and was present (blood pressure of over 160 systolic) in only a third of our cases.

Trauma was not a factor in the development of any of the lesions discussed here though it may produce aneurysms that are called "false" because the wall is made up of surrounding structures rather than dilated, thinned-out artery wall itself.

PATHOLOGY

With the exception of 2 cases of common-iliac aneurysm, all these cases involved the lower abdominal aorta, and in no case were the renal arteries involved in the aneurysm. In 5 cases there was aneurysmal involvement of the common iliac arteries as well as the aorta. An associated diffuse dilatation and elongation of all vessels, including the proximal aorta, was usual and represents a reminder that these aneurysms are manifestations of a generalized arterial disease. Associated arteriosclerotic occlusive disease was not the rule, only 6 of the 21 patients showing a deficit in pedal pulses or symptoms of peripheral arterial insufficiency, and 8 of the 21 patients having electrocardiographic or clinical evidence of coronary-artery disease.

The aneurysmal dilatation of the aorta caused an

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increase in the length as well as the diameter of the aorta. This elongation commonly resulted in bowing of the aneurysm-containing aorta to the left, but in 2 cases the aneurysm presented as a right-sided abdominal structure through the small-bowel mesentery. All aneurysms were lined with rough, laminated clot of thickness up to 2 cm. There was commonly a considerable adjacent inflammatory response involving the vena cava, posterior peritoneum and small-bowel mesentery, especially in the larger aneurysms. Erosion of vertebral bodies was not seen.

Symptoms and Signs

The symptoms of aneurysm of the aorta or iliac artery, except those of hemorrhage, are the effect of pressure or inflammatory reaction on adjacent structures. If the aneurysm is small, symptoms may be absent. Thus, in a thin person, a painless pulsatile mass may be noted by the patient or physician before any other symptoms develop. As the mass enlarges or causes a surrounding inflammatory reaction, pain may range from dull, steady abdominal or lumbar pain to quite severe pulsating pain in these areas. In some patients the pain may be referred to the testicle or thigh. Others have complained only of the large abdominal "pulse" without considering it a pain, the sensation being unpleasant and making them justifiably uneasy. There is frequently an association of pain to movement or change in position.

All patients in our group of resections for unruptured aortic aneurysms had noted pain in the abdomen or back. The duration of the pain varied from two weeks to two years with an average duration of six and seven-tenths months.

An obvious pulsating mass in the upper abdomen was present on physical examination of all aortic aneurysms in this series. In 1 patient with an iliac aneurysm, this was most easily palpated on pelvic examination. The mass of an abdominal aortic aneurysm is quite characteristic and easy to identify when it is over 5 or 6 cm. in diameter. The nonaneurysmal aorta made prominent by tortuosity or lumbar lordosis is differentiated by its narrow width. Occasionally, a tumor or cyst of the pancreas or even a pendulous left lobe of the liver may be very difficult to differentiate from aneurysm and may give the impression of expansile pulsation.

X-Ray Study

If the diagnosis is in doubt, as it rarely is, an x-ray examination of the abdomen will frequently confirm the presence of the aneurysm by demonstrating calcium outlining portions of the wall. A lateral film may show this to greater advantage than an anterior view.

If doubt still exists, aortography may be carried out. This was performed in most of our earlier cases. We have since abandoned it as a routine procedure since the diagnosis is almost always quite clear without it, and involvement of the renal arteries making the lesion inoperable is exceedingly rare and is best ascertained at operation. Aortography is not without risk, and 1 of our patients had a retroperitoneal hemorrhage from disruption of an arteriosclerotic plaque at the site of puncture that required two transfusions.

Aortography is carried out through a needle inserted in the aorta through the lumbar region on the left and may be done under local or general anesthesia. It is important to delay a short time after injection of the dye since the velocity of flow through the aneurysm is slow because of the wide diameter of the stream. It is also important to be aware that most of an aneurysm is full of clot so that the lumen as demonstrated by the aortogram will not be as large as one might anticipate from the size of the palpable mass.

Natural History of Aneurysms

Aneurysms in general progress to either rupture or thrombosis if the patient lives long enough. Emboli may arise from the clot inside the aneurysm. In contrast to peripheral aneurysms, aortic aneurysms very rarely thrombose completely or give trouble from embolization to the vessels lower down. Their life history is rather one of progressive enlargement leading to rupture and death. Frequently, when the wall of the aneurysm fails, hemorrhage occurs by a very circuitous route through the laminated clot lining the aneurysm and the adherent tissues surrounding the aneurysm. For this reason many patients will have spontaneous arrest of the hemorrhage from a ruptured aneurysm and not bleed again for several hours or days. Occasionally, a patient may go for years without a second hemorrhage, but this is very rare.

In considering therapy for abdominal aortic aneurysm, one should, of course, know the prognosis in the untreated disease. Estes[11] studied 102 patients with abdominal aneurysm and found that 63 per cent of them eventually died of rupture, and 37 per cent of other causes. A third of his patients died within a year of discovery of the aneurysm, and two thirds by three and a half years. None survived for more than eight years. Kampmeier[12] found that 82 per cent of patients with abdominal aortic aneurysms died of rupture and that the majority died within six months from the time of onset of symptoms. The fact that these aneurysms are unstable lesions causing many deaths by rupture justifies therapy by major surgery.

Treatment and Results

For the past two and a half years, since our introduction to its feasibility by DeBakey, the treatment

of aneurysm of the abdominal aorta at the Massachusetts General Hospital has been resection and replacement with a homologous graft. These grafts are preserved by freezing and sterilized by irradiation in the manner described by Meeker and Gross.[13]

Twenty-one patients have been operated upon: 19 for aneurysms of the abdominal aorta and 2 for iliac aneurysms. Fourteen of the aortic cases were elective operations (Table 1); 5 of the aortic and the 2 iliac aneurysms required emergency surgery for rupture of the aneurysm (Table 2).

TABLE 1. *Nonruptured Aneurysms of the Aorta.*

AGE	SEX	DURATION OF SYMPTOMS	BLOOD PRESSURE	ANGINA	ELECTROCARDIOGRAPHIC CHANGE	DIAMETER OF ANEURYSM	TYPE OF GRAFT	FOLLOW-UP RESULT
yr.						*cm.*		
62	M	5 wk.	120/80	Present	Present	9	Cylinder	Patient living & well after 24 mo.
61	M	2 wk.	140/80	Absent	Absent	10	Cylinder	Patient living & well after 20 mo.
60	M	6 mo.	130/80	Present	Present	15	Cylinder	Patient died of coronary occlusion after 20 mo.
65	M	12 mo.	180/110	Absent	Absent	14	Bifurcation	Patient living & well after 5 mo.
64	M	2 wk.	190/108	Absent	Absent	9	Cylinder	Patient living & well after 2 mo.
67	M	15 mo.	110/70	Absent	Absent	8	Bifurcation	Patient living & well after 3 mo.
61	M	24 mo.	135/85	Absent	Absent	6	Cylinder	Patient living & well after 10 mo.
62	M	3 mo.	220/125	Absent	Absent	6	Cylinder	Patient living & well after 14 mo.
62	F	3 mo.	175/85	Absent	Absent	7	Cylinder	Patient living & well after 1 mo.
56	M	1 mo.	154/100	Present	Present	7	Bifurcation	Patient living & well after 8 mo.
76	M	12 mo.	135/75	Present	Present	11	Cylinder	Patient died of bleeding ulcer & coronary occlusion after 1 mo.
70	M	24 mo.	120/80	Absent	Absent	10	Bifurcation	Patient living & well after 14 mo.
83	M	12 mo.	140/80	Absent	Absent	14	Cylinder	Patient living & well after 13 mo.
50	M	3 wk.	235/140	Absent	Absent	8	Bifurcation	Patient living & well after 25 mo.

Twenty-eight months later shows that all but 2 patients in this group are alive. One died one month after operation of a bleeding duodenal ulcer and coronary occlusion, and a second died twenty months after operation of coronary occlusion. The cause of death was confirmed in both these patients by autopsy. In the first case the graft appeared unchanged except for surrounding fibrous-tissue organization. The two-year graft was slightly dilated and showed two smooth transverse folds as though it had "accordioned" either from elongation of the graft or contraction of the envelope of scar. It was smooth in its lining and well supported by fibrous tissue, showing no tendency to aneurysm formation. The remaining patients had no evidence of disorder in the graft and adequate peripheral circulation at the time of the last visit, though in 4 cases it was necessary, immediately after operation, to remove popliteal emboli that occurred during surgery. Such occlusion of the distal vessels can be eliminated by careful handling of the aneurysm, applying occluding clamps above and below the aneurysm early in the operation, and instilling dilute heparin solution (10 mg. in 50 ml. of isotonic saline solution) in the arteries beyond the occluding clamps.

There were 7 patients who were first seen because of rupture of aneurysms. Two were female patients, eighty and eighty-three years of age, who had ruptured iliac aneurysms. They did well after excision and graft. The other 5 were male patients who entered the hospital with ruptured aortic aneurysms. Immediate operation was carried out, with successful outcomes in 2 of the 5. Anuria or severe oliguria was an important contributing factor in all 3 deaths, and recent myocardial infarction was found at autopsy in 2.

All the ruptured aneurysms were large, being 10 to 15 cm. in diameter. This is in accordance with the findings of Crane[14] in a study of post-mortem material in which rupture was noted in only 1 of 26 aneurysms under 6 cm. in diameter but in 14 of 17 cases with an aneurysm diameter of 6 cm. or over. Also of interest is the fact that only 1 patient had symptoms before the rupture.

TECHNIC

In unruptured cases catheter-instilled spinal anesthesia is the anesthesia of choice because in addition to unusually good relaxation, this technic allows the blood pressure to be lowered, greatly increasing the ease of manipulation of the aorta. A ruptured aneurysm may require an anesthesia that can be more rapidly accomplished and is less likely to disturb a precariously compensated low blood volume. Thoracoabdominal incisions have not been found necessary,

a long mid-line or left paramedian incision providing adequate exposure. The aorta is exposed, reflecting the small-bowel mesentery and upper jejunum to the right. The structures covering the left side of the aneurysm are reflected to the left, which requires division of the inferior mesenteric artery at its origin. No bowel ischemia has been observed to result from severance of this vessel, which is frequently found to be already occluded by thrombus; however, circulation was re-established in the internal iliac arteries in all cases. Sacrifice of both internal iliac arteries in addition to the inferior mesenteric artery may lead to bowel necrosis.[15] In the exposure of the upper aorta the inferior mesenteric vein and left renal vein are identified and retracted upward. Proximal and distal control of the vessel is obtained, and the circulation is occluded before much manipulation of the aneurysm lest clot be dislodged. As previously mentioned, heparin is injected into the distal arteries. Care is taken during the resection to avoid injury to the adherent vena cava. Removal of large aneurysms is easiest if they are first opened and evacuated.

Although we have not encountered aneurysmal involvement of the aorta at the renal arteries, in 3 cases it was necessary to occlude the aorta temporarily above the renal vessels. In 2, this was required to control hemorrhage from a ruptured aneurysm. In 1 of these cases, control below the renal arteries was obtained after twenty minutes. The patient had no significant depression of renal function, but there was evidence of lower-spinal-cord injury in motor weakness of the lower extremities. This patient made a good recovery and is working at the present time but was unable to walk without crutches for a period of three months. The other ruptured aneurysm had a tear extending up beyond the origin of the left renal artery in the posterior aorta. Here, the aorta was occluded for seventy minutes while this tear was repaired and control below the renal arteries obtained; this patient had no evidence of renal or spinal-cord injury. In another case the aorta fractured at the level of the renal arteries with application of a clamp below them, and it was necessary to occlude the aorta above the renal vessels for fifty minutes to repair this injury. This patient also had no evidence of spinal-cord or renal damage.

If the bifurcation of the aorta is intact, cylindrical grafts of thoracic aorta can be used; being of large diameter, they more nearly approximate the size of the patient's abdominal aorta. This was possible in 8 of the unruptured and 1 of the ruptured aneurysms. A cylindrical graft is much easier to use than a bifurcation graft since there are fewer anastomoses and these are in larger vessels.

Anastomoses are made with everting running sutures in the larger vessels and interrupted or running sutures in the smaller (iliac) vessels. In 3 cases it proved easier to suture the lower ends of the bifurcation graft to the side of the external iliac arteries after the cut ends of the common iliac arteries, which were too poor to use, had been closed. This maneuver allows perfusion of the internal iliac arteries, which are important to bowel circulation. In no case did the severe arteriosclerosis of the aorta make the performance of a satisfactory anastomosis impossible although on several occasions heavily calcified artery had to be punctured with a towel clip or a heavy

TABLE 2. *Ruptured Aneurysms.*

AGE	SEX	DURATION OF SYMPTOMS	BLOOD PRESSURE BEFORE OPERATION	ANGINA	ELECTROCARDIOGRAPHIC CHANGE	DIAMETER OF ANEURYSM	TYPE OF GRAFT	FOLLOW-UP RESULT
yr.						*cm.*		
Aorta:								
64	M	28 hr.	80/40	Present	Present	10	Cylinder	Patient died of uremia 15 days after operation
54	M	4½ mo.	145/100	Absent	Absent	15	Bifurcation	Patient died of coronary occlusion 1 day after operation
57	M	2 hr.	0/0	Absent	—*	11	Bifurcation	Patient living & well after 22 mo.
66	M	4 days	140/80	Present	Present	12	Bifurcation	Patient died of coronary occlusion on 7th day
61	M	2 days	0/0	Present	Present	12	Bifurcation	Patient living & well after 7 mo.
Common iliac arteries:								
80	F	14 hr.	200/90	Absent	Absent	6	Cylinder	Patient living & well after 15 mo.
83	F	48 hr.	160/90	Absent	Present	6	Cylinder	Patient living & well after 24 mo.; graft thrombosed after 1 yr., but no ischemic symptoms.

*Not done.

straight needle used as an awl before sutures could be placed.

Discussion

The acceptability of this surgery as a treatment for abdominal aortic aneurysm depends on a surgical mortality that is significantly lower than that of the untreated lesion. In this small series there has been no operative mortality in the elective cases. Although all symptomatic aneurysms encountered were operated on, surgery was not recommended on very aged or poor-risk patients with small, asymptomatic aneurysms. This practice is based on the assumption that an asymptomatic aneurysm is a stable lesion, especially when not large. This assumption may be challenged since rupture is frequently the first symptom. Cooley, DeBakey and Creech[9] report a mortality of 18 per cent in a series of 84 elective resections in which the diagnosis of aneurysm alone was considered sufficient indication for surgery. In 50 elective resections, Bahnson[16] had an operative mortality of 12 per cent. Two of the 6 deaths were due to complications referable to the graft and would presumably be avoidable at the present time. Szilagyi, Smith and Overhulse[15] reported a mortality of 20 per cent in a series of 15 elective resections but believed that all their deaths were due to technical difficulties. As the operative procedure becomes standardized and the indications for elective resection are clarified, the mortality should fall below 10 per cent, and this major surgery considered no more dangerous than any major abdominal operation in a given patient.

A ruptured aneurysm is a rapidly lethal lesion, and the survival of 1 out of 7 patients with this disaster in Bahnson's[16] series; 7 out of 17 patients in that of Cooley, DeBakey and Creech[9] and 2 of 5 patients in our series is unquestionably an improvement over the natural survival of such patients. The high operative mortality here, however, is an additional incentive to perform operation at a time of election.

Conclusions

Aneurysm of the major vessels in the abdomen is a very dangerous condition — more lethal than many types of cancer, for instance. Resection of the aneurysm and arterial graft remove the danger of death from rupture and can be performed with a reasonable operative mortality. Few patients can be saved by surgery after rupture has occurred. In a patient whose general condition is reasonably good, the presence of an abdominal aneurysm is sufficient indication for resection. Small, asymptomatic aneurysms are best left and carefully observed if associated disease or great age makes the operative risk grave or the prognosis poor even in the absence of aneurysm. Resection and graft should be seriously considered even in the poor-risk patient if the aneurysm is large or symptomatic since the likelihood of rupture under these circumstances is great.

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CHANGING BLOOD PRESSURE IN AORTIC INSUFFICIENCY*

Its Clinical Significance

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BOSTON

MARKED changes in arterial blood pressure and peripheral circulation may occur during the life history of patients with aortic insufficiency. These changes reflect alterations in cardiac function and peripheral vasomotor activity. As such they may be the first clues to progression of the disease and the ultimate development of failure of the left ventricle.

Lewis[1] has emphasized the fact that the patient with aortic insufficiency is warm and flushed, with bounding arterial, capillary and venous pulsations, and that this is due to associated vasodilatation. He specifically excluded from this description patients with aortic insufficiency in the final stages of congestive heart failure, who, on the other hand, are cool and pallid. He did not comment on any alteration in blood pressure.

Observations on a case reported elsewhere stimulated this study.[2] The patient was cool and pale; the pulse was slightly bounding, but there was no capillary pulsation; he had the murmurs of aortic stenosis and insufficiency and a blood pressure of 120 systolic, 74 diastolic. He was thought to be in terminal cardiac failure from predominant aortic stenosis and finally died a month after examination. A regurgitant-aortic-valve defect measuring 0.4 sq. cm. and a regurgitant leak of 5 liters per minute were demonstrated by special cinephotographic studies of the post-mortem heart.

Despite this unexpected anatomic evidence of considerable aortic regurgitation, the patient was not vasodilated, had a nearly normal blood pressure and was similar to the patients with congestive heart failure excluded by Lewis from his description of aortic insufficiency. After these observations, specific alterations in blood pressure and peripheral circulation, related first to the development of congestive heart failure and second to its treatment, were noted in 3 patients with aortic insufficiency.

CASE REPORTS

CASE 1. L. C., a 37-year-old man, had a past history of rheumatic fever and a known heart murmur for many years. Frequent attacks of sweating and flushing and a blood pressure of 150/50-70 had been noted for many years. The clinical course and the progression of the disease are shown in Figure 1. When he was first seen in March, 1954, for consideration of surgery on the aortic valve the blood pressure was 150/40-0, with bounding capillary pulses and warm, flushed extremities. He had cardiomegaly but no symptoms of cardiac failure. Gradually progressive exertional dyspnea and paroxysmal nocturnal dyspnea followed a protracted respiratory infection with grippelike symptoms. Two months later, he showed a cool, dry skin, normal arterial pulsations, a blood pressure of 135/70 and a large heart, with aortic Grade 4 systolic and Grade 3 diastolic murmurs. Radiologic examination showed a heart that was 1½ times the normal size, with a calcified aortic valve and a rocking beat. The electrocardiogram showed hypertrophy of the left ventricle. He was digitalized over a 4-day period, with a rise in vital capacity, from 3.2 to 4.5 liters, a fall in circulation time, from 29 to 18 seconds, a fall in diastolic blood pressure to 0, an increase in sweating and disappearance of symptoms. Eight weeks later, however, after another respiratory infection, dyspnea became worse and sweating less, and the blood pressure rose to 110/80; the vital capacity fell again; and the circulation time became prolonged. Diuretics and hospitalization caused a brief return of diastolic blood pressure and circulation time to lower values, with a rise in vital capacity. But within a few weeks irreversible failure, with peripheral venous congestion and cardiac cachexia, developed. He died 8 months after the onset of symptoms, showing preterminally a shocklike state, with a blood pressure of 90/70. Autopsy confirmed the presence of free aortic regurgitation as the dominant lesion.

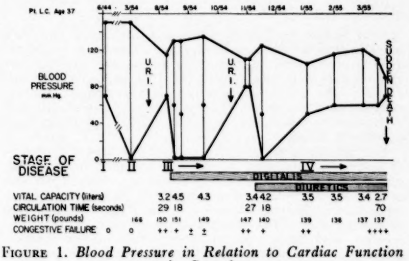
Pt. L.C. Age 37
6/54 3/54 8/54 9/54 10/54 11/54 12/54 1/55 2/55 3/55
BLOOD PRESSURE mm Hg
120
80
40
0
U. R. I.
U. R. I.
SUDDEN DEATH
STAGE OF DISEASE
I II III IV
DIGITALIS
DIURETICS
VITAL CAPACITY (liters) 3.2 4.5 4.3 3.4 4.2 3.5 3.5 3.4 2.7
CIRCULATION TIME (seconds) 29 18 27 18 70
WEIGHT (pounds) 166 150 151 149 147 140 139 136 137 137
CONGESTIVE FAILURE 0 0 ++ + ± ± ++ + ++ ++++

FIGURE 1. *Blood Pressure in Relation to Cardiac Function in Case 1.*

CASE 2. A.F., a 26-year-old man, was known to have a heart murmur from childhood. At the age of 17 he began to have attacks of dyspnea and cyanosis and to become weak on the slightest effort. On physical examination he had a bisferious pulse, cardiac enlargement, Grade 3 systolic and Grade 4 diastolic aortic murmurs, absent aortic 2d sound and a presystolic gallop. The aortic valve was seen to be calcified on fluoroscopy, and an electrocardiogram showed hypertrophy of the left ventricle.

The initial blood pressure was 120/100, and the vital capacity 1700 ml., and there was a systolic murmur, Grade 3 in intensity. The patient was then digitalized, with a fall in the blood pressure to 120/80, a rise in the vital capacity to 2400 ml. and an increase in intensity of the systolic murmur to Grade 5. Digitalis was then stopped for 6 weeks, with a rise in the diastolic blood pressure to 95, an increase in the circulation time from 20 to 28 seconds and a decrease in the systolic murmur to Grade 2. Redigitalization resulted in a fall in diastolic blood pressure to 80 (Fig. 2).

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CASE 3. T.B., a 22-year-old man, had rheumatic fever at 10 and again at 15 years of age, with persistence of murmurs ever since. He had attacks of sweating and tachycardia, ruddy skin, bounding arterial pulsations, cardiomegaly, with Grade 4 systolic and Grade 3 diastolic aortic murmurs and a mid-diastolic apical rumble, and a blood pressure of 220-300/0. The vital capacity, venous pressure and circulation time were normal. An electrocardiogram showed incomplete left-bundle-branch block. X-ray examination showed the classic findings of aortic insufficiency.

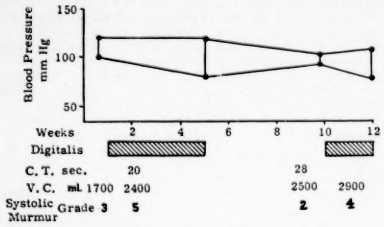

FIGURE 2. *Serial Blood-Pressure Changes in Case 2.*

Four months later marked dyspnea, orthopnea and chest pain developed. Cardiac findings were unchanged, but the arterial pulses were no longer so forceful, the skin was cool and the face pale, and typical blood pressures were around 150/50. The circulation time was now prolonged, and the vital capacity decreased. The patient was digitalized, with a decrease in circulation time and a fall in diastolic blood pressure to 160/0.

One month later he again entered the hospital because of increasing dyspnea, diffuse cardiomegaly, with a presystolic gallop and pericardial friction rub, a blood pressure of 130/40 to 165/20 and a large liver. Cortisone was administered in 500-mg. doses a day and then tapered to 100 to 150 mg. daily. The gallop and rub disappeared, the liver receded, sweating attacks returned, the circulation time decreased to 25 seconds, and the blood pressure returned to 150/0 (Fig. 3).

DISCUSSION

This study may be criticized because auscultatory pressures were used in 3 cases. Systolic pressures obtained by auscultation have been shown to be 83 per cent accurate as compared to direct readings,[3] but diastolic pressures are often read too low, especially in severe aortic insufficiency. Although the diastolic pressure may have been too low in relation to the exact reading, changes in this diastolic pressure were readily detected in all 3 cases by the auscultatory method. The purpose of this study primarily was to demonstrate, by a routine clinical method, changes in blood pressure in aortic insufficiency.

A fall in systolic pressure in aortic insufficiency, without a fall in diastolic pressure, usually indicates a fall in total stroke output. This was seen dramatically in Case 3, in which this pressure decreased from 300 to 150. Such a marked change in systolic pressure could only mean a decrease in stroke work and output of the left ventricle.

Although Wiggers[4] has challenged the concept that capillary pulsation is due solely to vasodilatation, the observations of Lewis[1] amply attest to the finding of earlier workers[5] that vasodilatation exists in aortic insufficiency. He pointed out that capillary pulsations and vasodilatation occur in "warm" normal persons, with fever, in thyrotoxicosis and in arteriovenous aneurysms just as in aortic insufficiency. In addition, he showed that patients with aortic insufficiency have warmer skin (and higher blood flows) than normal persons and that this pulsation and vasodilatation were independent of the magnitude of the pulse pressure, a finding supported by the observations of Salans et al.[6] of the unchanged form of premature beats in the central aortic pulses in aortic insufficiency. Finally, Myerson and his associates[7] showed that all the peripheral phenomena of aortic insufficiency, including disappearance of diastolic blood pressure, can be simulated in a single extremity dilated by intra-arterial mecholyl. Thus, the picture of low diastolic pressure, capillary pulsation and warm, flushed skin can be attributed not to the aortic regurgitation per se but rather to an associated vasodilatation.

If, however, a stimulus for vasoconstriction supervenes, these phenomena disappear. Lewis[8] demonstrated a rise in diastolic pressure with angina pectoris in some cases of free insufficiency, and he postulated vasoconstriction. Similarly, pulsatory phenomena are minimized with cold, and during the vasoconstrictor phase of the Valsalva maneuver, diastolic pressure rises in aortic insufficiency.[9]

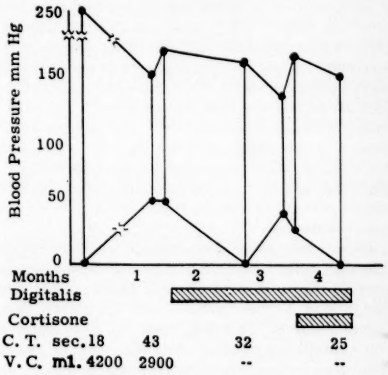

FIGURE 3. *Serial Blood-Pressure Changes in Case 3.*

In the 3 cases reported above, when congestive heart failure developed, diastolic blood pressure rose. Undoubtedly, with restriction of output or in relation to venous congestion,[10] systemic vasoconstriction predominated as in most cases of congestive heart failure.[10] Two patients (Cases 1 and 3) became clinically cool and pallid. In all 3 cases digitalization

resulted in a distinct fall in diastolic pressure. In Case 3 rheumatic carditis was successfully treated by cortisone, with a dramatic return of flushing and sweating attacks as well as a fall in diastolic pressure.

Thus, diminution in the peripheral signs of regurgitation and narrowing of the pulse pressure with an increase in diastolic pressure can serve as early signs of a change in circulatory status. If multiple daily observations demonstrate chronic pallor, cool skin, decreased capillary pulsations or increased diastolic pressure, so that transient variations due to environmental temperature, anxiety and so forth are excluded,* chronic vasoconstriction has superseded chronic vasodilatation. The major cause of this is failure of the left ventricle. Patients with aortic insufficiency may go for years without failure, but once failure sets in, the prognosis is gravely altered. As early indicators of downward progression of the disease, these changing signs have clinical value. Earlier digitalization and properly timed valvular surgery may perhaps be more readily effected. Conversely, reversal of these signs — the return of warm skin, bounding pulsations and a lowered diastolic pressure — will acknowledge the success of medical therapy in aortic insufficiency.

Summary and Conclusions

Three patients with predominant aortic insufficiency observed clinically before, during and after congestive heart failure are described.

The systolic pressure fell in 2 cases, and the diastolic pressure rose in all with the onset of failure. The diastolic pressure fell after therapy.

Peripheral circulatory phenomena of aortic insufficiency diminished in intensity in all patients during failure. These observations were explicable as follows: patients with predominant aortic insufficiency show peripheral vasodilatation, which is replaced by vasoconstriction when failure of the left ventricle develops.

The clinical value of serially recorded blood pressure in patients with aortic insufficiency is emphasized as a clue to incipient cardiac failure. The appearance of a narrowing pulse pressure should prompt immediate intensification of medical control and further attempts at definitive surgical correction, because of the grave prognosis once congestive heart failure becomes established in aortic insufficiency.

*Hemodynamic studies reported elsewhere have shown that changes in vascular resistance coincident with fear or anxiety can transiently raise the diastolic pressure in aortic insufficiency and lower it in pure stenosis, and temporarily limit the diagnostic significance of a given pressure reading.[2]

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MEDICAL PROGRESS

ALLERGY*

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BOSTON

ALLERGY is a word with many connotations. Approaches to its manifestations are multiple. It is hoped that the reader will be influenced by Florey,[1] who wrote in his first lecture on general pathology: "What do the observations, of whatever nature, that I make tell me about the disease process from which my patient is suffering? Never be intellectually satisfied with a diagnosis or a label." He advises all to amass data by observations and experiment, to amplify some points and to reject unworthy evidence. Such work by many will lead to the establishment of valid conclusions. Not everyone needs to work in a laboratory, but all should take the time to observe, collect and analyze.

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Basic Investigation

Antigens

Allergic diseases are assumed to be based on reactions between antigens and their specific antibodies.

Not all properties of antigens are fully understood, but some points appear to have been accepted. Most antigens consist in part of protein, but certain polysaccharides and lipoids in combination with carbohydrates can produce antibodies in mammals. After Landsteiner[2] developed haptens by uniting diazo-salts with proteins, it became possible to learn something about what makes an antigen specific. Important properties include the size of the chemical groups, their spatial arrangement, optical activity, number of amino acids and carboxyl groups at the end of the chain.

Antibodies

Two main hypotheses of antibody formation have developed. Breinl and Haurowitz[3,4] advanced the theory that antibodies are globulins and that their antibody properties are due to adaptation of their shape to that of the determinant group of the antigen. Such a theory requires the presence of antigen for antibody formation. Burnet and Fenner[5] believe that antigen must be present to start antibody formation but that once this process starts it can continue after the disappearance of the antigen. They think that once a cell develops knowledge of antibody formation it can impart such information to its daughter cells. Both groups agree that antibody is a modification of normal protein. Most evidence[6-9] supports the idea that the presence of antigen is needed for antibody formation. Obviously, neither theory has been proved.

Sites of Antibody Production

The exact site of antibody production has interested a host of investigators. Evidence has accumulated to support various hypotheses. Before these hypotheses are examined, it may be well to remember that most living cells possess the ability to produce protein. Most cells, therefore, which come in contact with antigen and secure it, can theoretically produce antibody. It is also necessary to remember that the production of antibody is no doubt a complex process and that several different types of cells may be involved.

For many years the ability of the cells of the reticuloendothelial system to engulf foreign particles has been known. Naturally, the reticuloendothelial system was considered as the site of antibody formation, and various technics have been used to show that the cells of the system do accumulate antigens. It has not been proved, however, that antibody is produced within these cells.

Burnet and Fenner[5] have reviewed thoroughly the evidence supporting the role of the lymphocyte in antibody production. Various experimenters have injected antigens in the foot pads of rabbits and studied the afferent and efferent lymph of the popliteal nodes as well as the nodes. Ehrich and Harris[10] found that the efferent lymph contained antibody and that the cells that they called lymphocytes contained five to seven times the concentration of antibody present in the fluid part of the lymph. Later, Ehrich et al.[11] preferred to call these cells lymphoid cells and not lymphocytes. Dougherty and White[12,13] showed that gamma globulin was a constituent of lymphocytes and that the adrenocortical hormones dissolved lymphocytes with the release of gamma globulin and antibody. Others[14-17] have questioned these data. The lymphocyte may play a role in antibody production, but just how important a role has not been determined.

Fagraeus[18] took red pulp and follicular tissue from rabbit spleens two or three days after the intravenous injection of antigens and grew each separately in tissue cultures. The red pulp, which was said to be mostly plasma cells, produced much antibody, whereas the follicular tissue, which was said to be mostly lymphocytes, produced little antibody. She concluded that the plasma cells come from the reticuloendothelial system and that the plasma cells are the main producers of antibody. Coons, Leduc and Connolly,[19] using fluorescent antigens, added evidence favoring the plasma cell as the producer of antibody.

The evidence supporting any site of antibody production is far from complete. The plasma cell appears to have the most supporters at present. It should be remembered, however, that the origin of the plasma cell is not explained and that there is no explanation why antigen, seized by cells of the reticuloendothelial system such as the Kupffer cells of the liver, should cause plasma cells to produce antibody.

Location

Much emphasis has been placed on dividing antibodies into those that are found in serum and those that are not, but recent work throws some doubt on this distinction. Chase[20] showed that leukocytes from tuberculin-sensitive guinea pigs could give rise to positive tuberculin reactions in nonsensitized guinea pigs. Others[21] have demonstrated passive transfer of reagins by means of leukocytes, and Lawrence[22] has transferred delayed skin sensitivity to streptococci by means of leukocytes.

Types

Early workers were greatly impressed by the differences in titer at which agglutination and precipitation occurred. This was construed to mean that different antibodies were produced in response to a single antigen. Gradually, another theory evolved, stating that a single antibody was produced for each single determinant in the antigen. Then, in 1936, this unitarian theory was supported by direct evidence[23,24] that agglutinin and precipitin to Type 1 pneumococcus were identical.

Evidence, which began to accumulate, suggested that the molecules of antibody formed in response to a single antigen were not always homogeneous. "Multivalent," avidly reacting or precipitable antibody and "univalent," low-grade or nonprecipitable antibody were postulated. Diversity in molecular weight and electrophoretic mobility were found by Kabat.[25] In the field of allergy, two nonprecipitating antibodies have been postulated, "skin-sensitizing" and "blocking."[26-29] These have not been universally accepted on either theoretical or practical grounds.[30] It has been suggested that under a restricted antigenic stimulus certain cells produce antibody globulin to their capacity, whereas if the stimulus is made multiple, other cells may also produce antibody.[31] This may account for some of the heterogenicity that has been noted.

Kuhns and Pappenheimer[32-37] found three antibodies when a single injection of 150 mg. of purified diphtheria toxoid was injected into Schick-negative human beings. These included the precipitating antitoxin, antitoxin reagin, which was capable of producing an immediate wheal reaction, and a "blocking" antitoxin, which protected against immediate reactions in previously sensitized skin sites. The reagin differed from the other antitoxins in being the only one to remain at skin sites for weeks and to produce a high serum titer for over a year.

Each new instance of diversity of antibody should be examined to make sure that it is not based on reasoning like that which seemed to prove that agglutinin and precipitin were different substances. An interesting example in a previously cited reference[30] is as follows:

> . . . The pretreatment serum will have a relatively low total antibody content, and most of the antibody will be in unmodified ("sensitizing") form. The post-treatment serum will have considerably more total antibody and much of it will be in the modified form . . . which fails to initiate the secondary reactions ("blocking" or "non-sensitizing") . . . the pretreatment *(low titer)* serum will lose its capacity to sensitize sooner [at a lower temperature], without being intrinsically more sensitive to heat, simply because it will be transformed gradually into modified, nonsensitizing form, while the post-treatment serum . . . will have to be completely denatured before it loses its only specific property of combining with antigen.

When more than one generalization seems compatible with the facts observed, the simplest one should be retained until it is proved inadequate.

Antibodies may vary in particle size, molecular weight, electrophoretic mobility, possible valency, firmness of union with antigen, avidity for union with antigen, avidity for union with complement and so forth. There is no close relation, however, between the physical and the serologic variations, and no reason to suppose that precipitins, agglutinins, opsonins and antitoxins differ except that the external circumstances and the testing method differ. Thus, the theory of unity of antibodies need not be discarded.

Combination of Antigen and Antibody

In recent years considerable work[38-43] has been done regarding the Arthus and Shwartzman phenomena. These two reactions had certain factors in common: injected skin sites showed perivascular accumulation of polymorphs; the injected skin areas accumulated lactic acid, and there was increased aerobic glycolysis; when the specific agent was injected to elicit either reaction, a leukopenia resulted; injected areas revealed leukocyte-platelet thromboses of capillaries and small veins; and these thromboses were followed by hemorrhage from these vessels. It was demonstrated that both the generalized and dermal Shwartzman reactions are prevented if heparin sufficient to produce noncoagulation of blood for four hours was given immediately after the provocative dose.

Burrage and Irwin[44,45] demonstrated changes in the small blood vessels of the lungs and livers of living mammals undergoing anaphylaxis. These changes included narrowing of the lumens of vessels, formation of emboli and thrombi, the closing of the outlet sphincters of the central venules of the liver and hemorrhages. Such factors are similar to those described by Stetson, Good and their associates in the Arthus and Shwartzman phenomena. It appears entirely possible that the microcirculatory vessels are involved during various allergic reactions.

Clinical Allergy

Some of the advances in basic investigation of allergy have been reviewed. Unfortunately, such investigations have not resulted in improvement in the care of allergic patients. Treatment is still based on removal of the allergic patient from offending antigens, on hyposensitization with crude preparations of antigens and on symptomatic therapy. Some advances have been made in methods of diagnosis and symptomatic therapy. A few will be considered. It is of interest that most of these advances are most useful in patients with symptoms of rhinitis, asthma, urticaria and eczema in whom the antigen-antibody reaction frequently cannot be demonstrated. It is evident that much careful work remains for the inquisitive physician.

Pulmonary-Function Tests

The testing of pulmonary function[46-50] in bronchial asthma has been in use for many years, but has not found general acceptance. The reasons for this lack of acceptance are not entirely clear, but an understanding of the problem may be found in an examination of the information to be gained and the methods used to obtain it. The purposes of testing pulmonary function in bronchial asthma are to determine the degree of disability of the patient, to follow the progress of the disease in individual cases, to provide

a means of direct testing of the pulmonary tree with suspected allergens, and to assay the effectiveness of various therapeutic drugs.

At the outset it should be made clear that pulmonary-function studies are intended to show physiologic deviations from the normal that may increase one's understanding of the pathologic process. They cannot determine the location or character of anatomic lesions.

The tests of pulmonary function employed in bronchial asthma include the vital capacity, maximum breathing capacity and index of intrapulmonary mixing of gases, as determined by the open-circuit or closed-circuit method. The studies of Baldwin, Cournand and Richards[51] have provided standard values in normal subjects.

The vital capacity is the maximal volume of gas that can be expelled from the lungs by forceful effort after a maximal inspiration.[52] It may be normal or decreased in patients with bronchial asthma as compared with the predicted normal.[46,48,49] Cournand[53] described a method of graphic registration of breathing by means of a modified basal-metabolism apparatus and noted that a change in the form of deep breathing, particularly retarded expiration, revealed early stages of pulmonary emphysema or bronchial asthma. More recently, Gaensler[54] has found that timed vital-capacity measurements provide a method for indicating the marked slowing of the expiratory phase commonly found in bronchial asthma and pulmonary emphysema. A subject in good health expires 80 per cent of the vital capacity in the first second.

The maximum breathing capacity is the maximal displacement of air in and out of the lungs in a given time (fifteen or thirty seconds). In this test, expired air is collected in a Haldane bag or Tissot spirometer. The figure is generally markedly reduced in bronchial asthma and pulmonary emphysema,[48,53] even in the absence of physical signs and symptoms. It is the most commonly used pulmonary-function test that takes account of the important time factor. The air velocity index[48] is based on percentage of predicted maximum breathing capacity divided by percentage of predicted vital capacity, the normal index being 1.0, and an index of less than 1.0 indicating a significant degree of bronchoconstriction.

Bronchial asthma is often accompanied by an increase in the residual volume and the functional residual capacity of the lungs (residual volume plus expiratory reserve volume). The residual volume is commonly determined by a study of the index of intrapulmonary mixing of gases.[55-59] The intrapulmonary mixing of gases is impaired when residual volume is increased. (After breathing 100 per cent oxygen for seven minutes, the alveolar air still contains more than the normal amount of nitrogen.) The uniformity of alveolar gas has been studied by Fowler[60] by means of a single-breath test. Analysis of expired air after inspiring oxygen showed variation in nitrogen concentrations above the normal (uniformity index) in patients with asthma. Intrapulmonary mixing of helium[61] has been used to show defective mixing of gases in asthma and in pulmonary emphysema.

Study of blood gases and pH have provided evidence of normal and abnormal oxygen saturation in subjects with bronchial asthma.[49,62] The rate of arterial oxygen saturation on inhalation of 100 per cent oxygen has been determined by means of an oximeter and found to be delayed in some patients with asthma.[63]

The findings obtained in a representative group of patients with bronchial asthma may be summarized as follows:

The vital capacity has generally been found to vary from normal to moderately reduced. For example, Herschfus et al.,[49] in 42 patients with asthmatic symptoms, found values ranging from 51 to 158 per cent of predicted normal values whereas Gaensler[48] reported the vital capacity to be reduced by 17.5 per cent in 9 asymptomatic asthmatic patients. However, vital-capacity determinations have proved to be of value in direct testing of the bronchial tree with aerosolized allergens[64,65] and in assaying therapeutic effects of bronchodilator drugs,[49,66-68] helium-oxygen mixture[69] and the corticosteroids and ACTH.[70]

The maximum breathing capacity has generally been found to be markedly reduced in bronchial asthma. In the cases of Herschfus et al.[49] the maximum breathing capacity varied from 11 to 130 per cent of predicted values. Baldwin[47] reported values averaging 58 per cent of predicted in 10 subjects during asthma-free intervals, and all improved after the use of a bronchodilator spray. Gaensler[48] found the maximum breathing capacity reduced by 58.8 per cent in 9 asymptomatic asthmatic patients. The value of this test is limited by the strenuous exertion for its performance — a difficult or impossible feat for a dyspneic patient with asthma. The timed vital capacity[54] has been shown to be a fairly satisfactory substitute for maximum breathing capacity.

The index of intrapulmonary mixing has been found to be markedly increased in bronchial asthma. The upper limit of normal is 2.5 per cent (percentage of nitrogen in the alveolar air). In Baldwin's[47] 10 subjects during the asthma-free interval the alveolar nitrogen was invariably high (the mean value for the group was 4.5 per cent). Herschfus et al.[49] reported the index of intrapulmonary mixing in 42 patients with active asthma to range between 1.0 and 12.2 per cent nitrogen.

The widespread applicability of tests of pulmonary function in patients with bronchial asthma is doubt-

ful at present because of the intricacy, cumbersomeness and expense of the equipment required and the experience needed for proper evaluation and interpretation of results. Personnel trained to carry out and interpret the tests are not widely available. Furthermore, in spite of the undoubted value of these tests in elucidating mechanisms of the pathologic process, as a diagnostic tool and as a means of measuring the effectiveness of therapy, clinical observation of the patient remains the most satisfactory method available to the average medical practitioner in the care of patients with bronchial asthma.

Drug Allergy

In contrast to the therapeutic nihilism so prevalent in the recent past, physicians are now beset with such a plenitude of "wonder drugs" that therapeutic measures are frequently adopted for even the vaguest symptoms. There has been a marked increase in reactions to these drugs; as Sir Francis Bacon said, "The remedy is worse than the disease." For, the unfortunate fact is that whereas all may be aware of the shortcomings of drugs, most continue to administer them for slight disturbance and often proceed with insufficient caution in patients whose history of previous abnormal reactions to certain drugs warrants a more careful approach. The diagnosis of hypersensitivity to drugs is not a simple procedure. There is no single test to determine the presence of drug allergy. Its manifestations can mimic any and all signs and symptoms of antigen-antibody union.

Antigenic capacity can be acquired by simple or crystalline substances of low molecular weight while in the process of being utilized with the body protein. It forms a complete antigen — that is, it is capable of producing and reacting with antibodies that result in an allergic state. Thus, after the newly formed hapten has sensitized the host, reactions can occur when the same, or chemically related, agent presents itself by the proper route. The simple drug confers specificity. Crossreactions frequently occur between chemically related drugs. The ability to form the quinone structure by simple oxidation is shared by sulfonamides, para-aminobenzoic acid, amino-azo dyes, aniline, aminophenol and paraphenylenediamine.[71] This confers the active principle that can be responsible for various allergic manifestations. Quinone structures are reactive and combine readily with human protein to form complexes of high molecular weight, thus forming antigenic agents. This group represents one of the most common of the crossreaction variety.

The potency of drugs as sensitizers varies greatly, depending not only on their own chemical composition but also on the degree, time and mode of a given person's exposure to them. Chances for becoming sensitized are increased along a line parallel to the increase in the armamentarium of drugs.

Immediate and delayed reactions are the two classifications into which symptoms fall, the latter being, by far, the more common. The most severe complication resulting from the administration of any given agent is acute anaphylactoid shock. This is, of course, quite easy to diagnose and, fortunately, most infrequent. It is characterized by cyanosis, prostration, weakness, dizziness, a drop in blood pressure, respiratory collapse and occasionally death, which may occur instantly or after several hours. Although serum sickness is no longer as prevalent as it once was, in its stead is a similar ailment brought about by hypersensitivity to drugs. Clinical manifestations, resembling serum sickness and resulting from sensitization, are caused by a union between the tissue component and the drug. As an aftermath of sensitization, it is not possible to predict the nature of the response that follows the administration of the drug.

Sensitizing and provoking doses may be administered in any of the usual ways. Unsuccessful attempts have been made to sensitize laboratory animals orally. A patient who undergoes direct external contact with a drug resulting in skin sensitization may suffer an occurrence of his dermatitis if the drug is administered orally.[72] Fixed eruptions may be sharply localized to only certain small areas of skin, which react upon systemic re-exposure. The sites themselves vary from patient to patient; nor can the reason for the peculiar localization be given.

Because experimental and therapeutic exposures do not always parallel one another, one can neither prove nor disprove that an unknown compound will produce an allergic reaction in therapeutic administration to man. Only by a clinical trial can it be determined whether or not a compound will have side reactions. A drug can be considered innocuous only after it fails to produce complications in a person who has previously been sensitized against a member of the same antigenic group. It is essential to measure the therapeutic usefulness of any drug against its side effects.

Penicillin today is one of the most widely used drugs and also one of the most allergenic. Each year an ever-increasing number and variety of reactions to it have occurred, from exceedingly mild urticaria to fatal anaphylactoid shock. It is a drug that has been proved therapeutically beneficial, with negligible toxicity, and yet allergenically potent. There is widespread use of penicillin, 350 tons being produced annually. Repeated exposures account for the large number of persons who are becoming sensitized to it.

The question has been raised of possible sensitization from sources that contain relatively small amounts of penicillin. Salk vaccine may contain 200 units per milliliter. When 16 adults[73] with known

respiratory allergic symptoms were subjected to intradermal and subcutaneous injection of the vaccine, no evidence of sensitivity was noted.

Of 474 samples of raw and pasteurized milk[74] tested for penicillin content, 55 (11.6 per cent) were found to contain from 0.003 to 0.08 units per milliliter. Anyone drinking 1 quart of the milk containing the maximum quantity would be getting 80 units of penicillin, most of which would be inactivated in the gastrointestinal tract. This could result in a reaction in a highly susceptible patient, but it is doubtful if it would sensitize a nonsensitive person.

In a series of 9 patients[75] with shocklike reactions to penicillin, all noticed some symptoms after 1 or 2 injections immediately before the one that produced the reaction, but they considered them too trivial to mention. The number of injections necessary for sensitization varied from 12 to 56, with a mean of 28.

Of 59 patients with anaphylaxis[76] due to penicillin, 55 were sensitized by procaine penicillin, 1 by neopenicillin, 2 by penicillin O, and 1 by an oral preparation. In anaphylactoid reactions recorded in 88 patients, 12 of whom had histories of previous penicillin sensitivity and 26 of whom were asthmatic or suffered from hay fever or other allergies, 23 proved fatal. An anaphylactoid reaction is more likely to develop in a person with a history of allergy.

One cannot predict, with any degree of certainty, how long the state of sensitivity will last. Although it appears that mild symptoms usually clear up sooner than more severe ones, they may persist for years or even develop into more serious ones.[77] Sensitization may subside even while the patient is still being treated with the drug, or it may occur in waves for a period of a month or two after the termination of its administration.

Crystalline and procaine penicillin seem to produce the same form and incidence of urticarial reactions. Penicillin in beeswax or oil causes a large number of reactions as well as irritations and reactions at the site of injection.[78] This may be due to the combined allergenic effect or the delayed absorption of penicillin.

Parenterally administered penicillin affords the most beneficial therapeutic results; when topically administered it is least effective, whereas oral administration lies somewhere in between. Sensitization, however, is more likely to occur when penicillin is administered topically, and least likely when it is taken orally. Lang and Clagett,[79] however, report the case of a fifty-three-year-old woman who, two hours after ingestion of a tablet (200,000 units) experienced numbness and tingling of the lips and eventually lost consciousness. The patient had previously received penicillin by parenteral and oral routes on several occasions without side effects.

There is no effective method of preventing allergic reactions to drugs, but conservative use will reduce the incidence. Therapeutic agents should be given only when there is clear-cut indication. Carr[80] stated that chemically the sensitizing potency of a drug is probably more significant than its potency as an elicitor, for a patient's only certain safety lies in not being sensitized in the first place.

(To be concluded)

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MEDICAL INTELLIGENCE

PORPHYRIN EXCRETION AND HEMOGLOBIN SYNTHESIS IN A CASE OF ACUTE INTERMITTENT PORPHYRIA*

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WASHINGTON, D.C.

RECENT advances in the knowledge of porphyrin biochemistry have shown that porphobilinogen is a normal intermediate compound in the synthesis of the protoporphyrin of heme.[1,2] Porphobilinogen results first from the combination of succinic acid and glycine to form δ-aminolevulinic acid; two molecules of this compound condense in turn to form porphobilinogen (Fig. 1).[2,4] As shown by the work of Gibson et al.,[5] porphobilinogen is the precursor not only of protoporphyrin but also of uroporphyrin and coproporphyrin. It has been suggested that uroporphyrin and coproporphyrin are by-products of the synthesis of protoporphyrin from porphobilinogen.[6] In another view, uroporphyrin and coproporphyrin may be precursors of protoporphyrin.[7] According to recent evidence[1,2] all these porphyrins arise by independent synthesis from porphobilinogen.

In the various clinical types of porphyria there are marked increases in the urinary excretion of uroporphyrin or coproporphyrin, and in the acute intermittent type, large amounts of porphobilinogen may be excreted as well. The appearance of these pigments in the urine is believed to be caused by overproduction.[8] In acute intermittent porphyria, attacks are frequently accompanied by increased excretion of porphyrins.[8] It is believed by some that the symptoms are produced by the porphyrins, perhaps through their effects on blood vessels.[9]

From consideration of what is known of the synthetic pathways of the porphyrins, it seemed that changes in the rate of synthesis of hemoglobin might also alter the rate of production of uroporphyrin and coproporphyrin. If these porphyrins are intermediates in or necessary by-products of protoporphyrin synthesis, increased hemoglobin formation produced by venesection might increase the excretion of uroporphyrin and coproporphyrin. On the other hand, if all the porphyrins are formed independently from porphobilinogen, venesection might so deplete the available porphobilinogen that less would be available for the formation of uroporphyrin and coproporphyrin. Transfusion should have the opposite effect.

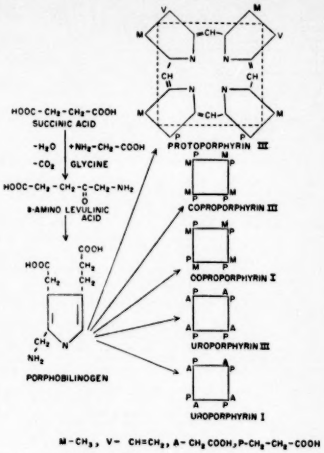

FIGURE 1. *Probable Pathway of Porphyrin Synthesis, after Shemin et al.[3] and Crosby.[2]*

METHODS

In a patient with acute intermittent porphyria 2000 ml. of blood was removed over a period of nineteen days. Subsequently, 2000 ml. of bank blood was given by transfusion. The clinical status of the patient was observed carefully during and after these procedures. The daily excretion of porphobilinogen, coproporphyrin and uroporphyrin was measured on specimens collected under refrigeration. Porphobilinogen was determined by the Watson–Schwartz[10] reaction, contaminating urobilinogen being removed by chloroform extraction and the color developed in a spectrophotometer being read at a wave length of 545 millimicrons against urobilinogen standards. The coproporphyrin method of Zieve et al.[11] was used. Uroporphyrin was estimated on a scale of one to four based on the fluorescence of the ethyl acetate extract from the coproporphyrin determination.[6] Frequent determinations were made of the hematocrit and reticulocyte count.

CASE REPORT

In June, 1954, a 21-year-old soldier, a former agricultural worker, experienced the 3d attack of undiagnosed abdominal pain. On this occasion porphobilinogen was found in the urine, and the diagnosis of acute intermittent porphyria was made. On admission to Walter Reed on De-

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cember 8 he had mild generalized erythema and diffuse tenderness of the abdomen that changed from day to day. There were no neurologic abnormalities initially, but after 2 months in the hospital, a coarse, persistent tremor of the hands developed. On February 9, 1955, he had an acute paranoid psychotic episode that lasted for approximately 1 week. Laboratory findings were entirely normal on repeated occasions except for the persistent excretion of elevated amounts of porphobilinogen, coproporphyrin and

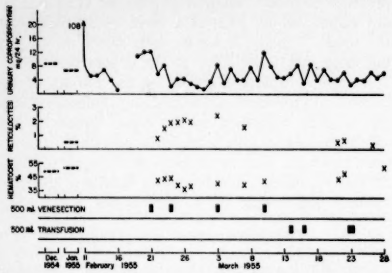

FIGURE 2. *Chronologic Data on a Patient with Acute Intermittent Porphyria.*

The dotted lines for coproporphyrin and hematocrit represent average values during the months indicated. The extremely high value of coproporphyrin occurred after the time of the acute psychotic episode.

uroporphyrin in the urine. The hematocrit was 44 to 53 per cent, and the Wintrobe erythrocyte indexes were normal. The reticulocyte count was less than 0.5 per cent, and the red-cell life span by chromium^{51}-labeling technic was normal (half life of 30 days). In February 2000 ml. of blood was removed from the patient over a 19-day period. Subsequently, 2000 ml. of bank blood was given by transfusion over a 10-day period. The daily excretions of porphobilinogen, uroporphyrin and coproporphyrin were followed in the urine, and frequent determinations of the hematocrit, reticulocyte percentage and clinical status of the patient were made.

The results of these experiments are shown in Figure 2; coproporphyrin excretion alone is indicated since the values for porphobilinogen and uroporphyrin showed similar variation at all times. Neither venesection nor transfusion produced significant changes in the coproporphyrin, uroporphyrin or porphobilinogen in the urine. The fall in hematocrit followed by the rise in the reticulocytes are taken as evidence that hemoglobin synthesis did increase after venesection; similarly, the reticulocytes fell after retransfusion, suggesting decreased hemoglobin synthesis. No clinical changes were observed during the study period. It is of interest, however, that the excretions of porphobilinogen, coproporphyrin and uroporphyrin were greatly increased 2 days after the acute psychotic episode of February 9 (Fig. 2). It is unknown whether the excretion rose before or after the onset of the psychosis.

Discussion

This patient appeared to produce hemoglobin at a normal rate. It may be estimated that he was forming 0.32 gm. of protoporphyrin a day.* From the normal response to venesection it may be reasonably estimated that the rate of hemoglobin synthesis was thereby increased threefold. If uroporphyrin and coproporphyrin are precursors or necessary by-products of protoporphyrin synthesis a threefold increase should therefore have occurred in their excretion. On the other hand, if all the porphyrins are derived from a single limited pool of porphobilinogen, there should have been a decrease of 0.64 gm. per day in the combined excretion of porphobilinogen, uroporphyrin and coproporphyrin. Although there may be other porphyrins or their metabolic products in the urine or other routes of porphyrin excretion, urinary porphyrin excretions should reflect such large changes of protoporphyrin synthesis as were produced if protoporphyrin metabolism is closely related to that of the abnormal porphyrins.

The results are better explained on the basis of the independent formation of all the porphyrins from porphobilinogen, if the amount of porphobilinogen that can be produced is unlimited. Another possible explanation is that protoporphyrin and the abnormal porphyrins are formed in different sites in the body from nonlimiting precursors. Porphobilinogen is formed at both sites, but once it escapes extracellularly, it cannot re-enter cells but must be excreted. Each site thus functions completely independently. There is some support for this hypothesis in the finding that porphobilinogen does not cross membranes readily.[13] This is essentially the concept of Watson,[8] who classifies clinical porphyria into two types, porphyria erythropoietica and porphyria hepatica, according to the site of origin of the abnormal porphyrins. In porphyria hepatica (of which the case reported above is an example) the abnormal porphyrins are produced in the liver. Thus, a change in hemoglobin synthesis in the bone marrow cannot effect utilization of porphobilinogen produced in the liver. An experiment similar to the one described here in porphyria erythropoietica occurs in nature in the hemolytic anemia that accompanies this disease. In several cases splenectomy corrected the anemia, and the porphyrin excretion decreased.[14,15] In this situation the production of red cells and the appearance of abnormal porphyrins seem to be coupled to one another.

*Whole blood = 15 per cent hemoglobin.
2000 ml. (blood removed) X 0.15 (fraction of hemoglobin) = 300 gm. of hemoglobin.
0.035 Hgb = porphyrin.[8]
300 X 0.035 = 10.5 gm. of porphyrin.

76 kilograms = patient weight; 8 per cent = estimate blood volume.[12]
6100 ml. = estimate blood volume.
910 gm. of hemoglobin 1 per cent produced per day normally.
1 per cent per day = 9.1 gm. per day.
9.1 X 0.035 = 0.32 gm. of porphyrin per day.

Summary

In a patient with acute intermittent porphyria the rate of hemoglobin synthesis was changed first by venesection and later by transfusion. These manipulations did not modify the urinary excretion of porphobilinogen, uroporphyrin or coproporphyrin. These results are regarded as evidence that the protoporphyrin of hemoglobin and the abnormal porphyrins arise independently and support the concept of separate sites of origin.

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CURRENT CONCEPTS IN THERAPY*

Penicillin

PENICILLIN is one of the most valuable and widely used drugs in present-day therapy. Its proper use is of utmost concern to everyone. Approximately 350 tons of the drug are consumed annually in this country. Substantial quantities are unfortunately used unwisely.

Pharmacology

Although its chemistry is known and it has been synthesized, the drug is still manufactured by the fermentation process. Many types of penicillin are possible, but for therapeutic purposes only two are used extensively enough to be considered in this summary. These are benzyl penicillin, or penicillin G, and phenoxymethyl penicillin, or penicillin V. Penicillin is a stable yellow powder that is soluble in water, in which it rapidly deteriorates. When it is introduced into the body over 50 per cent is found in combination with serum albumin, a fact that may predispose toward its allergenic properties. It is widely disseminated and appears in all cavities, but the concentration in the spinal fluid represents only a fraction of the serum level and even with high blood levels is usually below an effective amount. This can, of course, be altered somewhat by larger doses, which give a higher serum level, or in the presence of severe inflammation in the central nervous system, which permits a more ready passage of the drug. Usually, however, it is necessary to give the drug intrathecally to attain dependable action. Penicillin is rapidly excreted by the tubules of the kidney, and therefore a continuously replenished supply must be furnished to the blood stream or the level in the serum falls below effective concentrations. Certain drugs, such as probenicid, through blocking tubular excretion are effective in retaining the drug in the blood stream for longer periods.

*Prepared under the supervision of the *Journal's* Committee on Advertising.

Therapeutic Use and Value

Penicillin is primarily effective against gram-positive organisms. It is highly effective, however, against the gram-negative gonococcus and meningococcus, and is also effective against actinomyces, borrelia, spirillum and treponema. For the most part, little tolerance or resistance to it has been developed by the streptococcus, pneumococcus, gonococcus or meningococcus. The staphylococcus, however, has in a high percentage of cases, especially those found in hospitals, developed a high degree of resistance.[1] Penicillin has no effect against common viral infections such as the acute upper-respiratory-tract infections, viral pneumonia and influenzal infections.

Its merit as an effective prophylactic in preventing acute gonococcal infections and when given over long periods in preventing the recurrence of rheumatic fever is widely accepted. However, its routine use as a prophylactic after surgery, in communicable diseases, viral infections and many other situations where it is presently given as a prophylactic measure is for the most part of little value and frequently proves harmful.[2]

Toxic Properties

Although penicillin is one of the safest drugs known, it can have serious toxic effects. Over 200 serious anaphylactic reactions and 50 deaths have been reported as a result of penicillin sensitivity. All but 2 of these serious reactions have followed parenteral administration. Urticaria develops in approximately 6 per cent, serum-sickness-like reactions in 0.1 per cent, and hepatitis, agranulocytosis, necrotizing angiitis and other rare but serious complications in occasional patients. Unfortunately, the serum-sickness type of reaction and urticaria may not occur until ten days or so after the drug has been discontinued and once present may persist for long periods. When the drug is applied topically skin

sensitivity occurs in 10 per cent or more; therefore, its use in this way should be abandoned.[3]

Dosage

The dose of penicillin depends upon organism sensitivity, type of infection and status of the patient. In overwhelming infections in a seriously ill patient aqueous penicillin G sodium given intravenously as a continuous infusion in a total daily dose of 1,000,000 to 50,000,000 units may be required. Most infections are well controlled by a daily dose of 800,000 units, usually given intramuscularly, in two 400,000-unit doses of procaine penicillin G in aqueous suspension — 300,000 units combined with 100,000 units of penicillin G sodium. In cases in which it may be desirable to have a very long-acting repository penicillin, 300,000 to 600,000 units of benzathine penicillin G (Bicillin) may be given. Since blood levels with this preparation are low it should not be used in the treatment of acute or severe infections. Its chief role is as a long-acting prophylactic, as in the treatment or prevention of streptococcal throat infection, in which antibiotic action for ten days or more is desirable. Its oral use has little merit.

Route of Administration

Since the oral route is far safer than the parenteral it is much more desirable. Fortunately, in a high percentage of situations the oral route is entirely satisfactory and should be utilized. For oral use, buffered sodium or potassium salt of penicillin G, usually 200,000 to 400,000 units (120 to 240 mg.) every six hours given on an empty stomach, is satisfactory. The more recently introduced acid-stable penicillin V given in a dose of 200,000 to 400,000 units (125 or 250 mg.) at intervals of four to six hours is effective and can be administered irrespective of meals. It is resistant to the acid stomach juices, gives good blood levels and undoubtedly is a very effective but as yet expensive preparation for oral administration.[4] Undoubtedly, oral penicillin therapy should replace parenteral therapy wherever possible.

Preparations Available

Finally, a word should be said about combinations of penicillin with other preparations. As with other excellent agents, there is little or no merit in the combinations of penicillin with streptomycin, sulfonamide or other drugs in fixed ratios. For best therapeutic results the drug should be adjusted to the needs of the patient. When given as a fixed component of a multiple-ingredient preparation proper dose adjustment may be difficult or impossible. The use of penicillin in combination with other antibiotics, antihistamines, aspirin, sulfonamides and vitamins and in foods, toothpastes and vaccines is undesirable. In combination with aspirin and antihistamines, in which the parent preparation is for the most part used in treating the common cold, penicillin can be of little or no value, and at the same time in susceptible persons serious reactions or an allergic state may result. This unwise use of penicillin may preclude its future use in the patient thus sensitized.

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CASE RECORDS
OF THE
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CASE 42281

PRESENTATION OF CASE

A sixty-four-year-old man was admitted to the hospital because of anuria.

Ten days previously he noted "soreness" in the lower abdomen associated with anorexia. Three days later the urinary output began to decrease gradually until he became anuric four days before entry. There were intermittent episodes of nausea and vomiting with vague, poorly defined pains in both lower quadrants of the abdomen. Catheterization of the bladder on the day of admission failed to yield urine. There had been no change in the color of the urine before the patient became anuric. There was no history of renal calculi, gravel in the urine, prostatism, flank pain or exposure to nephrotoxins.

Mild asymptomatic hypertension had been known to be present for several years. Eight months before admission there was a transient episode of weakness and numbness of the left side of the body. An appendectomy and right-sided inguinal herniorrhaphy were performed twenty-three years before admission.

Physical examination showed a well nourished, oriented man in no distress. There was no edema. Examination of the optic fundi revealed some narrowing of the vessels, with increased light reflex but no papilledema, hemorrhages or exudates. The heart was not enlarged. There was a normal sinus rhythm at a rate of 88. The aortic second sound was greater than the pulmonic. A Grade 1, precordial, systolic murmur was audible. Examination of the abdomen revealed healed appendectomy and inguinal-herniorrhaphy incisions. The liver, spleen and kidneys were not palpable. There was no tenderness. Rectal examination showed the prostate to be normal in size and consistence. Peripheral pulses were good. Neurologic examination was negative.

The temperature was 99°F., the pulse 80, and the respirations 14. The blood pressure was 164 systolic, 94 diastolic, in the right arm and 184 systolic, 110 diastolic, in the left arm.

Examination of the blood revealed a hemoglobin of 10.5 gm. per 100 ml. and a white-cell count of 9700. The sedimentation rate was 54 mm. per hour. The nonprotein nitrogen was 90 mg., the total protein 5.9 gm., the albumin 3.6 gm., the globulin 2.3 gm., the phosphorus 6.7 mg., the calcium 8.8 mg., and the creatinine 8.3 mg. per 100 ml. The sodium was 123 milliequiv., the potassium 5.2 milliequiv., the chloride 85 milliequiv., and the carbon dioxide 24 milliequiv. per liter. The pH was 7.47. The alkaline phosphatase was 3.3 units. An x-ray film of the abdomen demonstrated two calcifications lying above the ischial spine on the right; some calcification was noted in the region of the prostate; the right kidney was larger than the left; there were degenerative changes in the lumbar spine.

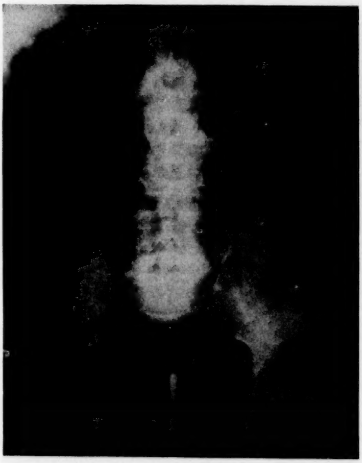

FIGURE 1. *Plain Film of the Abdomen with the Ureteroscope and Ureteral Catheters in Place.*
Calcification is present at the tip of the right catheter. The left kidney is somewhat smaller than the right.

Upon catheterization of the bladder 60 ml. of clear, straw-colored urine that gave a + test for albumin was obtained; the specific gravity was 1.007, the pH 6, and total solutes 215 milliosmols per liter; the sediment contained 50 crenated red cells, 1 or 2 white cells and no casts per high-power field; culture showed no growth. An attempted retrograde pyelogram revealed bilateral ureteral obstruction so that only the distal portion of each ureter could be catheterized; no opaque medium was injected; the tip of the right ureteral catheter lay just inferior to the most medially placed calcification previously noted opposite the ischial spine (Fig. 1).

On the second hospital day an operation was performed.

Differential Diagnosis

Dr. Richard Chute*: May I see the x-ray films?

Dr. C. C. Wang: The abdominal film taken at the time of admission shows a few gas-containing loops of small bowel. The kidney outlines are well seen on both sides; the left kidney appears normal in size; the right kidney may be somewhat larger than usual. There are no stones in either kidney. Two rounded calcifications are noted in the right side of the pelvis just above the ischial spine. A retrograde pyelogram demonstrates a small amount of contrast medium in the right upper urinary tract. The calyxes outlined appear somewhat dilated. The previously noted calcific densities in the right side of the pelvis appear to lie outside the right ureter, which is not dilated. The tip of the catheter on the left lies probably at the ureterovesicular junction.

Dr. Chute: In the protocol the left kidney was described as definitely smaller than the right; do you agree with that?

Dr. Wang: It is slightly smaller than the right, but I think both are fairly normal in size.

Dr. Chute: The predominant clinical feature, which brought this patient to the hospital, was oliguria that was becoming anuria. In the absence of a definite history of recent prolonged exposure to or ingestion of some nephrotoxic agent such as carbon tetrachloride, which would make acute renal failure a virtual certainty, the first thing to do in any case of oliguria or anuria, especially in a man of sixty-four, is to rule out obstruction of the lower urinary tract by catheterizing the bladder. If no urine is found in the bladder, it is obligatory to investigate the upper urinary tract, to ascertain the presence or absence of obstruction, to note the excretion of urine from each kidney, or the lack thereof, and to gain information about the situation. A certain number of persons, as a result either of disease or of a developmental anomaly, have only one functioning kidney. These procedures were carried out. The bladder was catheterized and found to be empty. Then cystoscopy was performed, and ureteral catheterization attempted. Obstruction, which could not be passed, was met a very short distance up each ureter, and on the right side the shadow of a probable ureteral calculus lay at the tip of the catheter. Thus, bilateral ureteral obstruction is a very possible cause of this patient's anuria.

Before we go farther in this case, we should discuss possible causes of oliguria or anuria other than obstruction. What was introduced and is perhaps best known under the term of lower-nephron nephrosis (also called acute renal failure and most recently acute tubular necrosis) is a well known and unfortunately not too uncommon cause. This may be brought on by intravascular hemolysis as a result of hemolytic transfusion reactions or of transurethral prostatic resection when distilled water used for irrigation has entered open venous channels. It may also be precipitated by crushing injuries to muscle, by circulatory collapse and resulting renal ischemia from any cause by nephrotoxic substances such as mercury and carbon tetrachloride and by sulfonamide-sensitivity reactions. However, none of these etiologic factors of lower-nephron nephrosis (or acute tubular necrosis) seem to have been present; therefore, I believe that it can be ruled out.

Occlusion of the renal artery, usually produced by a sterile embolus secondary to fibrillation in rheumatic or arteriosclerotic heart disease, will result in infarction of the kidney and, if bilateral or in a solitary functioning kidney, which is very rare, will cause anuria. Thrombosis of the renal veins, if bilateral, is another cause of anuria. This is usually associated with septic states or extension of thrombosis of the femoral or iliac veins into the vena cava to involve the orifices of the renal veins. Forty per cent of cases occur in infants under one year of age. Other rare causes of oliguria or anuria are bilateral renal cortical necrosis, bilateral renal papillary necrosis, periarteritis nodosa, acute glomerulonephritis and even dehydration of extreme degree. In the case under discussion, it seems to me that there was no evidence that the anuria of four days' duration was due to any of the conditions that I have just mentioned. A final cause of oliguria or anuria is chronic progressive renal disease, which, I believe, played a part in this case.

The facts that examination of the abdomen revealed no tenderness, that the white-cell count was 9700 and that the temperature and pulse rate were only barely elevated make me believe that there was not any acute intraperitoneal lesion or septic process. A dissecting aneurysm of the aorta could block off one or both renal arteries to give anuria, but a patient with such a process would have had a great deal more pain and would have been much sicker than this patient was. The finding that both the systolic and diastolic pressures were considerably higher in the left arm than in the right arm makes one wonder if the patient had an aneurysm of the aortic arch or even a tumor, interfering with the blood flow in the right innominate artery. However, such an aneurysm or tumor would probably cause a contracted pupil and a mass seen in the x-ray film of the chest. There is no mention of such findings, so I shall say that there was simply a nonpathologic disparity in the size of the arteries concerned.

The laboratory data suggest chronic progressive renal insufficiency. Apparently, some urine passed into the bladder after the initial catheterization, for

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another catheterization produced 60 ml. The red blood cells in this specimen suggest that the urine came from the right side, where the ureteral calculus was, and that it escaped past the stone. (I am taking it for granted that there was a stone.) This urine suggests that the kidney's function was not good because it was quite dilute (specific gravity of 1.007 — even more dilute than plasma, which has a specific gravity of 1.010) and contained an abnormally small amount of total solutes — only 215 milliosmols per liter. It was "lighter" in total solutes than normal plasma, which averages 285 milliosmols per liter. Not only was the nonprotein nitrogen elevated to 90 mg. per 100 ml. but also the creatinine was markedly elevated to 8.3 mg. over a normal of 1.1 mg. Such an elevation of creatinine indicates not only serious nitrogen retention but also the probability that this was not just an acute affair but a serious progressive chronic condition. Retention and consequent elevation of the serum phosphorus are common in uremia, and are usually accompanied by a falling serum calcium level, as in the case under discussion. The low sodium and chloride may have been caused by a salt-losing nephritic process, and the loss of chloride by vomiting. The hemoglobin of only 10.5 gm. per 100 ml. would fit in with the secondary anemia of chronic renal disease.

When I read in the protocol that the left kidney was smaller than normal, I reasoned that the left kidney's function was almost nil and that it was either a hypoplastic kidney (which I now see from the x-ray films it could not be at its size) or, more likely, contracted and shrunken as the end result of an old pyelonephritis. Possibly, it had played some part in causing the hypertension. I believe that probably the right kidney, obstructed by a stone on admission, had previously been performing practically all of this patient's renal function, but that even before it became obstructed by the calculus, it was performing it none too well, because it, itself, was the victim of chronic progressive renal disease. What the inability to pass a ureteral catheter up the left ureter meant, I do not know. There was no shadow suggesting stone. Perhaps the ureter was truly obstructed — perhaps not. It could have been acutely obstructed by an extrinsic mass such as a tumor. However, if it had been chronically obstructed, I should expect a hydronephrosis, which would have given an enlarged renal shadow, rather than a small one. On the other hand the fact that the right kidney was obstructed may account for the fact that it was larger, and perhaps the left was normal in size.

It is my opinion that the left kidney was smaller and functionless and that the right kidney not only was blocked by a ureteral calculus, the immediate cause of the sudden anuria and pain in the lower abdomen, but also had poor function because of chronic progressive renal disease. I hope the patient survived the operation.

DR. AUSTIN L. VICKERY: Dr. Baker, you saw this patient when he was first admitted to the hospital.

DR. MYLES P. BAKER: I have nothing to add except that he was sent to the hospital by his physician in the middle of a severe snowstorm. He spent four hours in the ambulance, which broke down en route. I think that is an indication of his innate toughness.

DR. JACOB LERMAN: I should like to ask Dr. Chute about the stone in the ureter. I gather that the x-ray film demonstrates that the stone was outside the ureter.

DR. CHUTE: One of the shadows was outside the ureter, but I think the medial one touched the ureteral catheter. However, it is disconcerting not to see the ureter above it dilated.

DR. WANG: The right ureter is fairly well seen and is not dilated. I think that the two calcifications are outside the ureter. If it was inside it did not cause obstruction.

DR. ELBERT P. TUTTLE: It is difficult to evaluate someone else's report of a urinary sediment, but when I looked at the sediment of the urine it did not suggest long-standing chronic renal disease. There were no casts; the very few red cells were fresh and may well have been the result of trauma to the bladder during catheterization. Cystoscopy had not been done before we looked at the sediment. My impression was that there had been recent obstruction, first on one side and then on the other. I believed that there was probably an extraureteral obstruction.

DR. CHESTER M. JONES: Has Dr. Chute any suggestion about why the catheter did not go beyond the bladder on the left side?

DR. CHUTE: No, except that it met obstruction.

DR. JONES: It would suggest obstruction on the left side as well as on the right.

DR. CHUTE: Bilateral obstruction, yes. Of course, as in the playing of golf, what one man can do with a certain club, another cannot. Sometimes, the catheter may be too stiff and catch in a fold, but I am taking at face value the statement that the catheter could not be passed by an obstruction.

DR. LERMAN: I recall a patient whom I was asked to discuss in whom the obstruction came from a downward growth of a tumor of the pancreas, by which both ureters were obstructed. That is also unusual. The more common type of tumor that obstructs ureters is tumor from the prostate that extends upward.

CLINICAL DIAGNOSIS

? Extraureteral obstruction of unknown etiology.
? Ureteral calculus.

DR. RICHARD CHUTE'S DIAGNOSES

Ureterolithiasis, right.
Nonfunctioning left kidney.
Chronic progressive renal disease.

Anatomical Diagnosis

Periureteric fibrosis, bilateral, with ureteral obstruction.

Pathological Discussion

Dr. Vickery: Dr. Howard I. Suby treated the urologic aspect of this man's problem. Since he is not here today, I shall take the liberty of abstracting his operative note. This was an exploration of the right kidney and ureter. The upper ureter was found to be embedded in dense, firm tissue, which grossly appeared highly suspicious of carcinoma. However, a pathological consultation was not diagnostic for tumor after a frozen-section preparation. Consequently, a nephrostomy tube was placed in position; after a catheter had been threaded from the lower pelvis of the kidney downward, the ureter was freed from the mass. Microscopically, the mass was fibrous fatty tissue that showed a sclerotic process containing indifferent inflammatory cells, principally lymphocytes and mononuclear cells (Fig. 2). There was no

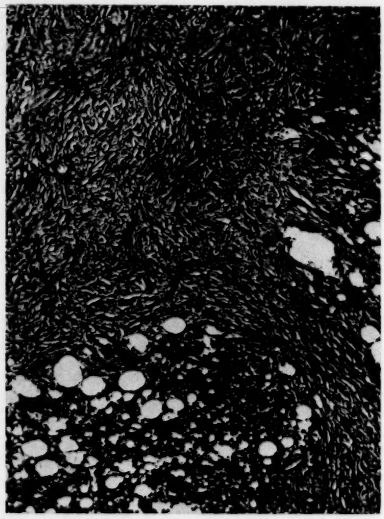

Figure 2.

evidence of neoplasm. This was considered to be an active fibrotic process, with chronic inflammation of obscure etiology. At a subsequent operation a month later the opposite ureter was explored and presented essentially the same type of picture — a peculiar form of localized, retroperitoneal fibrotic process surrounding a lower segment of the ureter.

As you probably have surmised, when the pathologist comes to a conference armed with volumes from the library, the diagnosis is probably unusual, as in the case under discussion. In the literature a similar entity is described. This condition was first reported in 1948 by Ormond[1] under the title, "Bilateral Ureteral Obstruction Due to Envelopment and Compression by an Inflammatory Retroperitoneal Process." Ormond described 2 patients with this odd lesion who had experienced sudden anuria without antecedent urinary difficulties. He had no explanation for the genesis of the process, and the mechanism was considered to be unknown in these first 2 cases. Since this report 7 additional cases have been reported, the last 3 of which were recorded under the title of "Bilateral Symmetrical Periureteric Fibrosis," by Raper[2]; his account sums up the general problem quite succinctly:

> The disease seems to originate as an inflammatory process in the region of the main vessels of the posterior abdominal wall. A very invasive fibrosis occurs, which may surround and penetrate the ureters as a result of which they are pulled toward the midline and compressed and finally occluded. The early stage of the disease is vague and insidious, but it proceeds to its climax rapidly as uremia or anuria develops.

This author also warned that successful ureteral catheterization and retrograde pyelography do not necessarily rule out this lesion. Consequently, he asked whether or not this peculiar fibrotic process, by enveloping the periphery of the still patent ureter, somehow interferes with its peristaltic movement and whether this may be related to the subsequent anuria in certain cases.

The case under discussion, then, constitutes the tenth reported occurrence of the rare lesion. I hope that we shall still be friends, Dr. Chute.

Dr. Benjamin Castleman: Dr. Baker, what has happened to this patient?

Dr. Baker: He has been quite well. Dr. Suby hopes that he will be able to close the nephrostomies soon.

Dr. Castleman: He had nephrostomies on both sides?

Dr. Baker: Yes.

Dr. Tuttle: He has now put out 1 liter of urine a day through one of the ureters. (I think it was the right one.) Several procedures to rectify the artificial drainage system have been carried out, but now I understand the nephrostomy tube is out on one side and he has passed into the bladder more than 1 liter of urine a day.

Dr. Castleman: What is the nonprotein nitrogen?

Dr. Tuttle: The serum creatinine came down to 1.6 mg. per 100 ml. The glomerular filtration rate was 60 to 70 per cent of normal and remained there when adequate amounts of sodium were supplied. There have been a couple of bouts of fever with infection.

References

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2. Raper, F. P. Bilateral, symmetrical, peri-ureteric fibrosis. *Proc. Roy. Soc. Med.* **48**:736-740, 1955.

CASE 42282

Presentation of Case

A forty-nine-year-old man was admitted to the hospital because of "phlebitis."

Two years previously there was an episode of Bell's palsy on the left. Ten weeks before entry the patient noted painful red streaks measuring 3 to 5 cm. in the calf of the left leg, with swelling, tenderness and erythema of both legs. Subsequently, involvement of the right arm and then the left arm occurred. With bed rest, Priscoline and Diamox therapy some of the swelling subsided. Because of persistent pain in the legs and arms that was increased with motion or with walking, he was forced to stop working. A transient episode of diplopia was noted three weeks before entry. At this time x-ray films were said to have shown a questionable osteolytic lesion of the left hip. Three days before admission he noted vertigo in a clockwise direction associated with some retching. He was given Thorazine. Seven hours before entry ptosis of the right eye and dilatation and irregularity of the right pupil were noted. There was a loss of 26 pounds in weight during the three months before admission and anorexia for two months before entry. During this time "arthritis" had been noted in the left hip. There was no history of hematemesis or melena.

Physical examination showed a pallid, obtunded man. There was no lymphadenopathy. Two small, purpuric spots were seen on the inner margin of the lower lip. Five splinter-shaped hemorrhages were noted in the nail beds of the hands. There were no Osler nodes. There was ptosis of the right eye. The right pupil, which was regular and did not react to light or on accommodation, measured 4 mm. in diameter. The left pupil measured 2 mm. in diameter and was normally reactive. Facial weakness on the lower left was noted. Slight abduction of the right eye was possible. There was impaired upward and downward gaze, with fair lateral and medial gaze on the left. The optic fundi were normal. Examination of the heart showed a normal sinus rhythm. The point of maximal impulse was 1 cm. beyond the midclavicular line in the fifth left interspace. The aortic second sound was greater than the pulmonic. A short, Grade 2, apical, systolic murmur was audible. Examination of the abdomen revealed a sense of resistance in the epigastrium; no definite mass could be outlined. The liver edge, which was slightly tender but not definitely felt, was percussed 2 fingerbreadths below the xiphoid. The spleen was not palpable. There was definite swelling of both lower extremities, with + to ++ pitting edema. Multiple fibrosed veins were felt in the right antecubital fossa, the right wrist, the right popliteal space and the left calf; these were not tender except in the right wrist. Weakness of the left arm and leg, especially on extension, and questionable weakness of the right leg were noted. There was bilateral plantar extension.

The temperature was 101.4°F., the pulse 88, and the respirations 14. The blood pressure was 120 systolic, 75 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 10 gm. per 100 ml. and a white-cell count of 20,500, with 90 per cent neutrophils. The platelets were normal. A sternal-bone-marrow aspiration was normal. The serum nonprotein nitrogen was 25 mg., the total protein 6.2 gm., the albumin 4.3 gm., the globulin 1.9 gm., the bilirubin 0.5 mg., and the fasting blood sugar 123 mg. per 100 ml. The serum sodium was 141 milliequiv., the potassium 3.6 milliequiv., the chloride 101 milliequiv., and the carbon dioxide 24 nilliequiv. per liter. The serum pH was 7.48. The amylase was 6 Russell units, and the lipase 0.96 ml. The alkaline phosphatase was 5.4 units. The total acid phosphatase was 2.4 units, and the prostatic 1.2 units. The prothrombin content was 26 per cent. Cephalin

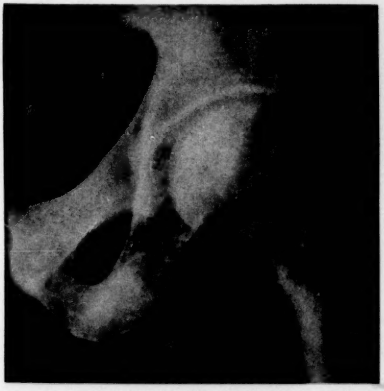

Figure 1. *Anteroposterior View of the Left Hip, Showing Lytic Destruction of the Ischium Involving the Tuberosity and Inferior Margin of the Acetabulum.*

flocculation was negative, as was the Coombs test. Six blood cultures showed no growth. A lumbar puncture yielded 6 ml. of clear acellular fluid at an initial pressure equivalent to 70 mm. and a final pressure equivalent to 30 mm. of water; the Pandy test was negative; the total protein was 62 mg., and the sugar was 93 mg. per 100 ml.; the gold-sol curve was 0111-110000; a culture and the Hinton test were negative. X-ray films of the skull and chest were normal. Films of the left hip demonstrated an area of bone destruction in the left ischium extending from the tuberosity to the inferior margin of the acetabulum; some bone density was present within the area of rarefaction (Fig. 1); little, if any, periosteal reaction was identi-

fied; an abdominal film was normal except for the defect noted in the ischium. An upper gastrointestinal series showed a smooth, rounded impression over the entire course of the lesser curvature (Fig. 2). An electrocardiogram showed a normal sinus rhythm at a rate of 100; the PR and QRS intervals were 0.16 and 0.08 second respectively; there was left-axis deviation; the T waves were low in Leads 1 and aVL and inverted in Leads 3 and aVF; the P waves were prominent.

On the third hospital day the petechiae in the lower lip were no longer present. The patient became increasingly obtunded, responding only to painful stimuli. In spite of penicillin and streptomycin therapy the temperature ranged between 99°F. and 104°F., and the white-cell count between 20,500 and 35,200. On the eighth hospital day massive edema with increased heat was noted in the right leg and thigh. Peripheral pulses were good. One observer felt a nodular liver edge 1 fingerbreadth below the xiphoid. The nonprotein nitrogen gradually rose to

FIGURE 2. *Roentgenogram from a Gastrointestinal Series, Showing Extrinsic Pressure upon the Lesser Curvature of the Stomach.*

136 mg. per 100 ml. The blood ammonia was 43 microgm. per 100 ml. A fibrinolysin test showed complete lysis of the clot after six hours at room temperature.

An operation was performed on the tenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. MORTON N. SWARTZ*: In coming to a diagnosis in this case I shall be obliged to put together signs and symptoms dealing with the venous system, the digestive tract, the skeletal system, the central nervous system, the cardiovascular system and the coagulation mechanism.

This patient's illness began with what appears to have been thrombophlebitis involving segments of the superficial veins of the arms and legs. Pain on walking was sufficiently troublesome to force him to leave work. The pain may have been the result of reflex arterial spasm since the peripheral pulses were noted to be good on later examination. Recurring thrombophlebitis may be associated with thromboangiitis obliterans. However, the suddenness of onset, the absence of evidence of primary arterial disease and the fact that the larger superficial veins, rather than the smaller veins of the hands and feet, were involved, make Buerger's disease quite unlikely.

About a century ago, Trousseau pointed out that patients with visceral carcinoma are prone to develop thrombophlebitis involving multiple superficial veins. This association appears primarily with mucinous carcinomas. Carcinoma of the body or tail of the pancreas is the most common one, but carcinoma of the stomach, lung, gall bladder or rectum may also be associated with this phenomenon. Such thrombophlebitis is usually resistant to anticoagulant therapy. For the moment, then, my attention is directed toward the possibility of a malignant process. The anorexia and marked weight loss suggest a neoplasm of the stomach or body of the pancreas. May we look at the films?

DR. PAUL M. G. ST. AUBIN: The chest and skull series show no abnormality. A gastrointestinal study reveals a mass extrinsic to the stomach impressing the lesser-curvature aspect throughout its length and displacing the stomach laterally and anteriorly (Fig. 2). The mucosal pattern is normal, and the duodenal bulb shows a deformity in its middle portion without evidence of ulceration. The duodenal loop appears intact, and on a number of the films the right lobe of the liver appears enlarged. No abnormal calcification is noted in the abdomen. The extrinsic pressure defect on the lesser curvature could be the result of an enlarged left lobe of liver or, more likely, a mass in the tail of the pancreas.

A film of the pelvis shows an area of patchy bone destruction, involving the body and descending ramus of the left ischium with loss of the cortex in one area (Fig. 2). This appearance is consistent with an osteolytic malignant process.

DR. SWARTZ: The lytic lesion of the ischium is what one might expect with metastasis from carcinoma of the stomach or pancreas or from a hepatoma but not from carcinoma of the prostate. The slightly elevated serum acid phosphatase and prostatic phosphatase is the only reason for considering a prostatic neoplasm. Primary hepatic neoplasms could produce caseous metastases, such as were seen here. As a rule, however, hepatomas arise on a background

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of cirrhosis. The normal serum albumin and globulin levels and the negative liver-function tests are against the diagnosis of cirrhosis. There is nothing in the history to suggest acute or chronic liver disease.

The episode of Bell's palsy two years before admission may not have been related to the present illness. It would be helpful to know if the facial palsy cleared up completely. Seven weeks after the onset of thrombophlebitis, evidences of neurologic disturbance appeared. There was peripheral third-nerve involvement on the right as well as some involvement of the sixth nerve on the same side. The left hemiparesis suggests a lesion of the right cerebral hemisphere (middle cerebral artery). There was also involvement of the third and fourth cranial nerves on the left. The complete right-third-nerve paralysis was not a pressure phenomenon in view of the normal optic disks and the normal spinal-fluid pressure. Multiple cerebral emboli or thromboses seem the best explanation for these findings. With multiple metastases one might expect increased intracranial pressure. Rare cases of embolic occlusion of blood vessels in brain and other organs by tumor emboli have been reported.

This patient presented some evidence of cardiovascular disease. The Grade 2, apical, systolic murmur may have been significant. The electrocardiogram was reported as showing prominent P waves; however, there was no auscultatory evidence of mitral stenosis. There was no atrial fibrillation — a possible basis for multiple emboli. The splinter hemorrhages in the nail beds and the purpuric spots on the lower lip suggest the small peripheral emboli seen in bacterial endocarditis. The physicians caring for this patient also considered this and drew blood for many cultures, which were negative. The fever, anemia, anorexia and weight loss also suggest this diagnosis. The white-cell count was rather high for subacute bacterial endocarditis, but it may be elevated in this disease in the presence of peripheral emboli and infarctions. The rising nonprotein nitrogen could be associated with "embolic nephritis." The nodular liver, the lytic lesion of the left hip and the multiple peripheral venous thromboses, however, are extremely difficult to explain on the basis of bacterial endocarditis alone.

Finally, we have evidence of several defects in the coagulation mechanism. The prothrombin content was only 26 per cent of normal. Also, there was significant evidence of fibrinolytic activity of the serum. It would be of help to know if the fibrinogen level was also reduced, as may occur with certain fibrinolysins or in the presence of intravascular fibrin thrombi. Fibrinolytic activity of the serum may occur in several situations: cancer of the prostate, in which tumor actually releases an active fibrinolysin; cancer of the pancreas, in which trypsin or similar proteolytic enzymes are released and activate the profibrinolysin of plasma; shock; certain obstetric complications; after lung surgery; and in liver disease. Gross bleeding was not a problem in this case, however. Platelets were normal, and so thrombotic thrombopenic purpura seems unlikely as an explanation for the multiple thromboses.

In summary I believe that the various manifestations may be tied together. The patient had carcinoma of the body of the pancreas, explaining the anorexia and weight loss. Metastatic lesions were present in the left ischium and the liver. Thrombophlebitis migrans was related to this carcinoma. It is thought that the excess trypsin released into the circulation from these tumor cells produces multiple thromboses. These thromboses may also occur in arteries and capillaries, perhaps explaining some of the cerebral signs and also the renal failure. Multiple intravascular fibrin thrombi may lower the plasma fibrinogen level and also activate plasma fibrinolysin. The fever and leukocytosis are consistent with a severe case of phlebitis migrans. The splinter hemorrhages and some of the cerebral lesions could be explained by small emboli from a nonbacterial thrombotic endocarditis. This has been reported in association with phlebitis migrans and visceral carcinoma.

DR. LEONARD ATKINS: Dr. Ellis, will you tell us the opinion on the ward?

DR. DANIEL S. ELLIS: I was asked to see the patient and to do a liver biopsy if I believed that one was indicated and that it would help in the diagnosis. By the time I saw the patient he was completely unresponsive. After ascertaining this much I must admit that I did not do a careful neurologic examination and devoted my attention primarily to examination of the abdomen. It was very easily determined that this patient had a large, hard, nodular mass in the epigastrium, which appeared to be within the abdomen and very close to the abdominal wall. It is my recollection that the Service believed that he had an expanding intracranial lesion with evidence of an osteolytic neoplastic process in the ischium. I agreed that there was also a neoplastic mass in the upper middle portion of the abdomen. I could not be sure that it was in the liver. However, the liver was so hard, firm and close to the visceral surface of the abdominal wall that I had no hesitancy in doing a needle biopsy. I did the biopsy without having to use any preoperative medication or even any local anesthesia. A very satisfactory specimen was obtained, which was white and crumbly and grossly appeared to be consistent with what we have seen so often when we have biopsied a mass of carcinoma. I did not believe that there was any clinical or laboratory evidence to support a diagnosis of primary parenchymal liver disease such as hepatitis or cirrhosis.

CLINICAL DIAGNOSIS

Metastatic carcinoma of liver.

Dr. Morton N. Swartz's Diagnoses

Carcinoma of body or tail of pancreas, with metastases to liver and left ischium.
Thrombophlebitis migrans, superficial veins.
Nonbacterial thrombotic (marantic) endocarditis.
Occlusion (?embolic) of right middle cerebral artery, with multiple infarctions (embolic or thrombotic) involving brain stem.
Multiple capillary thrombi, kidney and brain.

Anatomical Diagnoses

Cholangiocarcinoma of liver, with metastases to lymph nodes, peritoneum and bone.
Nonbacterial thrombotic endocarditis, mitral valve, with embolism and infarction of spleen and brain, recent.
(Thrombophlebitis migrans, superficial veins.)
Phlebothrombosis, femoral veins.
Meningitis, acute.

Pathological Discussion

Dr. Atkins: The biopsy of the liver that Dr. Ellis obtained showed a well differentiated adenocarcinoma. We could not be certain of the primary site on the basis of the biopsy specimen. The patient died a week later. At autopsy the liver weighed 2100 gm. and contained a firm, yellow, infiltrating tumor that measured 10 cm. in diameter and occupied most of the right lobe of the liver. The gall bladder and cystic duct could not be definitely identified grossly because of infiltration of this region by tumor and fibrous tissue. Microscopical sections of the region of the gall bladder showed normal gall-bladder mucosa as well as tumor in the surrounding tissue. It was our belief that the tumor probably arose in one of the smaller biliary radicles of the liver, although a primary site in the gall bladder or cystic duct could not be absolutely ruled out. The hepatic and common bile ducts, as well as the pancreas, were normal. There were widespread peritoneal implants of tumor, as well as metastases to the bones and retroperitoneal lymph nodes.

The heart was not enlarged; a friable, nonbacterial vegetation that measured 6 by 3 mm. was found on the free edge of the mitral valve; otherwise, the valves were normal. As suggested by Dr. Swartz, this case is an example of so-called "marantic" endocarditis that is sometimes associated with carcinoma or a debilitating disease. There were emboli to the spleen, where a small recent infarct was found, and also to the cerebrum. Both femoral veins were occluded by organizing thrombi. Dr. Richardson will describe the brain.

Dr. Edward P. Richardson, Jr.: There were numerous recent infarcts in the cerebral hemispheres on both sides, most extensive in the right, where virtually the entire hemisphere was softened. The oldest-appearing part of this infarction was in the right parietal cortex. A small lesion of the same nature was found in the tegmentum of the midbrain on the right, involving the area occupied by the fibers of the third cranial (oculomotor) nerve in their course from the nucleus to the periphery. Microscopical examination showed several typical emboli in a number of arteries, including the right anterior cerebral artery, and in small branches from the upper end of the basilar artery, so located as to provide an explanation for the midbrain infarct described. In addition, there was recent thrombosis of a number of large veins overlying the cerebral hemispheres with adjacent foci of recent cortical necrosis that could be attributed to these venous occlusions. Within the subarachnoid space, especially abundant over and in the ventricular system, there was an acute purulent exudate containing innumerable polymorphonuclear leukocytes. Thus, the patient had terminal acute meningitis as well. There was no evidence of metastatic carcinoma in the brain.

The third-nerve palsy and left-sided hemiparesis with which the patient was admitted to the hospital can be explained by the infarction in the right side of the midbrain and in the right cerebral hemisphere respectively. As additional infarction occurred and later meningitis and venous thrombosis, the neurologic signs became bilateral, and the patient was deeply comatose.

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EVALUATION SERVICE FOR GRADUATES OF FOREIGN SCHOOLS

A PARADOXICAL situation exists in American medicine today, one that is familiar to most active practitioners. Whereas the teachers, training facilities and research opportunities in medicine are surpassed by none in the world, many general hospitals cannot be provided with recent American graduates as interns or residents, and many state mental institutions are in desperate need of professional staff personnel. Both factors have played a part in the influx of foreign-medical-school graduates in recent years. Evaluation of the training and competence of these visiting or immigrant doctors, as well as of American graduates of foreign schools, has been a difficult and annoying problem to all concerned and especially to boards of registration in medicine.

The Board of Trustees of the American Medical Association has approved a long-sought program for evaluating the acceptability of these graduates of foreign medical schools and has also approved a plan for the administration of the program. The program and plan presented by the Cooperating Committee on Graduates of Foreign Medical Schools* were approved in principle by the House of Delegates at its recent meeting.

The Massachusetts Board of Registration in Medicine has been painfully aware of the problems in evaluating, in the manner set forth by the statutes of the Commonwealth, the training of such applicants for registration. Whether this new plan of the American Medical Association will facilitate the Board's deliberations remains to be seen. If all hospitals and teaching units in the Commonwealth agree to accept as interns, residents, fellows, or students only graduates of foreign schools whose training has been approved by the "Evaluation Service for Foreign Medical Graduates," *limited* registration of these doctors will become a simple and routine matter. So far as training is concerned, the statutes require for limited registration only that the applicants have "creditably completed not less than three and one-half years of study in a legally chartered medical school having the power to grant degrees in medicine." All the determinations regarding the legal charter, the power to grant degrees in medicine and the creditable completion of the three and a half years of study will have been made by the "Evaluation Service" before the doctor enters this country. Making these determinations for those trained in countries now behind the Iron Curtain has severely strained the resources, imagination and credulity of the board members in the past, and relief from this responsibility will be welcome. However, it is at present doubtful if all hospitals will agree to accept only those approved by the "Evaluation Service"—the urgency for obtaining interns will undoubtedly foster sidetracking in some

*Report of Council on Medical Education and Hospitals. *J.A.M.A.* **161**:159-161, 1956.

cases. In fact one of the principles guiding and directing the Cooperating Committee was an understanding that establishment of an "Evaluation Service" "should not interfere with a hospital's privilege of making its own selection among qualified physicians."

Another of the same principles, that the "Evaluation Service" should not "serve as a substitute for or interfere with the normal licensure procedures of the various state boards," makes it obvious that solution of the many vexing problems in *full* registration of graduates of foreign medical schools in Massachusetts will not necessarily be facilitated by the work of the "Evaluation Service."

Many physicians in the State may not be familiar with the most recent amendment to Section 2, Chapter 112, of the *General Laws,* as amended by Section 1, Chapter 396 of the *Acts* of 1945. This most recent amendment, approved and signed by Governor Herter on August 1, 1955, reads as follows:

> In the case of an applicant who has received from a medical school legally chartered in a sovereign state other than the United States or Canada the degree of doctor of medicine or bachelor of medicine or its equivalent, his qualifications shall be reviewed by a committee consisting of two members of the committee on medical education of the Massachusetts Medical Society appointed by the president of the Massachusetts Medical Society, one member of the committee on education of the Massachusetts Osteopathic Society, and the deans of the medical schools in Massachusetts; and this committee shall certify to the board when, in their opinion, the qualifications of such applicants are equivalent to those required of applicants who have graduated from approved medical schools in the United States or Canada; and in the case of an applicant so certified the board *may,* upon payment of twenty-five dollars by said applicant, then *admit him to the examination for licensure.*

The organization and effective operation of the committee established by this amendment has been delayed by many problems: no funds provided for secretarial help; no salaries provided for those asked to take on tedious chores; and no provision for substitution by a busy dean of a representative from his faculty.

It seems quite likely that the committee might, in some cases, derive substantial help from the "Evaluation Service" if the findings of the Service are made available to it. In many, however, the old problems of verifying educational requirements will remain. The "Evaluation Service" does set a precedent for a screening examination for these applicants, and this will surely help.

At present, these difficulties are the more significant when one realizes that most of the applicants unfortunately fail the examinations miserably when they are permitted to take them. A great deal of tedious work and time yield the Commonwealth very few acceptable practitioners.

The statutes of the Commonwealth, as interpreted by the Attorney General, will continue to determine eligibility for registration in medicine in Massachusetts. The use of discretion on the part of the Board becomes possible only when the statutory requirements have been fulfilled. These statutes are the work of legislative bodies and apparently are not ideal in the minds of many physicians because the advisability of recommending certain changes in them is under study by a committee on registration of the Massachusetts Medical Society. This is a worthy effort and should be a continuous one. Meanwhile, derogatory criticism of the Board's decisions by applicants and their partisans unfamiliar with the statutes simply discourages conscientious public service.

CURRENT THERAPEUTIC CONCEPTS

In the past decade numerous new drugs, drug combinations and therapeutic technics for the treatment of various diseases have appeared. These vary in value from the highly desirable to those of questionable or no merit. Unfortunately, the volume of these therapeutic claims is so great that it is nearly impossible for the busy physician to find time to study and evaluate them properly. Frequently, agents are introduced before there is much in the literature to support the claims made. Furthermore, many of the new substances or procedures are so complicated or so technical that special knowledge of the particular field is required to form sensible opinions concerning their values. As a result, a very undesirable situation has come into being whereby many physicians find themselves increasingly dependent on the claims of pharmaceutical-house detail men and the advertising that appears in such profusion in the medical journals and the mail.

Undoubtedly, the highly ethical pharmaceutical firms, through their representatives and advertising, endeavor to make available all information about their products. They are also alert to detect any defects or toxic properties of their agent and to pass on this information promptly to the physician. Each firm, of course, endeavors to place its own products in the most favorable light and avoids, as a matter of policy, criticizing as inferior or rating as better a competitor's product even when such information may be available.

This, then, leaves it up to the physician to discover the actual truth on his own. He can do so in one of three ways. In the first place, he can spend enough time and effort to become proficient in the field and then read the literature on the particular substance or technic. Unfortunately, becoming proficient may require a review of basic science courses, such as pharmacology, and complete coverage of the literature may be equally difficult since much of the written material may not be printed in the readily available journals.

The physician can use the new drug or technic and decide about the merits of the treatment by trial

and error on his patients. This, of course, is highly unsatisfactory since it can be detrimental to the patients, as well as expensive, and, unless the treatment is frequently used, it may be nearly impossible to form a sensible opinion. Unfortunately, this procedure is too often followed, leading to the widespread use of nearly worthless technics and medications. Under such a program, drugs with nothing more than placebo value can be widely accepted and used for long periods before the true picture becomes apparent. Furthermore, such a procedure can be harmful both to the prestige of the physician and to the patient's welfare. A drug with inherent toxic properties may cause much damage before adequate knowledge is obtained by this type of study.

Finally, there is a third way in which the physician can approach this perplexing problem. He can be very conservative about his use of new drugs and procedures until they are widely accepted among leaders in the medical profession and authorities in the special fields as evidenced by articles in the leading clinical journals and confirmatory studies by independent investigators. He can accept, as the best available opinion, articles prepared by the Council on Pharmacy and Chemistry of the American Medical Association and editorial articles appearing in the leading journals. Admittedly, this is the best procedure to follow, but, unfortunately, pressures are great, time limited, and needs urgent when therapeutic measures are considered.

There is, consequently, a most serious need for help in this field. The measures already carried out by the Council on Pharmacy and Chemistry and the many articles and editorials on therapeutic matters are excellent, but they are not always current and certainly there is not nearly enough of this type of writing.

This situation has created concern in the minds of many. There have been many requests that an effort be made to give additional, up-to-date guidance in therapeutic matters. The hope has been expressed that some program or procedure could be established whereby information current among those with special knowledge in various therapeutic fields could be made available to those who are in urgent need of it.

The Committee on advertising of the *Journal* has, during the past year, gained a great deal of experience in its dealings with the many new preparations, claims and types of information that are being presented to physicians everywhere. Consequently, it seemed to many that this committee was a logical group to undertake the task of organizing and maintaining, with the help of a wide group of consultants, a column in the *Journal* in which current concepts of therapy would be presented and queries concerning drugs and procedures might be answered so far as possible. The first of these articles appears elsewhere in this issue of the *Journal*.

VIRUSES IN SEARCH OF DISEASE

Newly devised technics and their widespread application under a variety of conditions have often resulted in a host of new discoveries. This was well illustrated in the field of microbiology, in which the development of bacteriologic technics led to the discovery of large numbers of different microbes and their identification with specific pathologic entities. In the process numerous additional bacteriologic entities were found to which no such causal relations could be ascribed. Even now the human respiratory and gastrointestinal tracts are replete with large numbers and varieties of living and cultivable bacterial species that in their host play a role other than that of producing disease; the presence of some of them may, indeed, be essential for the healthy state of their hosts. On the other hand, certain species like *Escherichia coli* have long been recognized as major components of the fecal flora, but their role as pathogens specifically related to outbreaks of diarrhea has been appreciated and proved only in the last few years.

The current developments and improvements in technics of tissue culture and their application to the cultivation and identification of viruses are now having an effect similar to that of the early use of the methods of isolation, cultivation and identification of bacteria. Other fortuitous circumstances have contributed to the rapidly accelerating developments in the virus field. The discovery of the Coxsackie group of viruses was made possible by the use of suckling mice, just as the use of chick embryos had earlier simplified the search for other viruses, notably the group now known as myxoviruses (the viruses of influenza, mumps, Newcastle disease and others). Intense interest in the viruses that cause poliomyelitis and in the development of vaccines against this disease has been generated by the National Foundation for Infantile Paralysis. The generous support given by that foundation and by other agencies to investigators interested not only in poliomyelitis but also in other viral diseases has permitted many experienced workers to concentrate on fundamental problems in this field. Many new viruses have been encountered, particularly in fecal material but also in cerebrospinal fluid, in the course of investigations of poliomyelitis and of infections simulating that disease. Meanwhile, other new and previously unrecognized viruses were demonstrated through the cultivation of adenoidal tissues from apparently healthy persons, and some of these agents were demonstrated by other methods in certain infections of the respiratory tract.

These recent contributions made by Enders, Dalldorf, Rowe, Huebner, Hilleman, Sabin and their respective associates, as well as those of many others who are making rapid strides within this field, were the subject of a two-day conference on the general subject, "Viruses in Search of Disease," held at the

New York Academy of Sciences late in May. The interest in this field is reflected in the fact that nearly 400 workers from all over the United States and some from other countries sat through five long sessions listening to presentations of new data, reviews of old data and discussions of various aspects of these new agents.

The material was organized around three large groups of viruses — namely, the Coxsackie group, the adenoidal-pharyngeal-conjunctival or respiratory-infection group and the so-called enteric cytopathogenic human-orphan group. The isolation and characterization of increasing numbers of antigenically distinct types of viruses in the course of various studies and under a variety of circumstances were detailed. Some of the biologic properties of these agents and certain methodologic and nosologic problems also came under discussion.

Many useful facts emerged in addition to the clarification of a number of previously confusing problems. Several of the so-called orphan viruses — that is, agents that had been isolated but had not been definitely identified with disease entities in their original hosts — have now been related with varying degrees of firmness to some entities or have since shown evidence of having produced infection in some hosts. Some specific types of new viral agents have been identified as causes of aseptic meningitis and of cases previously labeled nonparalytic poliomyelitis. These, of course, are in addition to such viruses as those of mumps and lymphocytic choriomeningitis already known to be associated with such infections. Intensive studies of various groups of cases of nonbacterial meningitis or of nonparalytic poliomyelitis during certain poliomyelitis seasons are yielding definitely identifiable viruses in increasing proportions of cases. Most such strains have turned out to belong to Coxsackie Group B, but some strains of Group A Coxsackie viruses and others from at least one of the prototypes of the enteric cytopathogenic human-orphan (E.C.H.O.) group have also been implicated.

Some cases of isolated myocarditis, or of infection in which myocarditis is a major component but in which infection by bacteria or by other known viruses has not been implicated, have also been identified with certain types of Coxsackie viruses.

Most of the specific types of adenoidal, pharyngeal, conjunctival and respiratory-infection viruses have now been implicated in certain types of infection, including the acute undifferentiated respiratory disease of military recruits, certain nonbacterial types of exudative pharyngitis, certain specific types of nonbacterial conjunctivitis — epidemic keratoconjunctivitis in particular — and other illnesses in which conjunctivitis is only a part of a respiratory or a more generalized infection. Herpangina and pleurodynia in its various forms had already been specifically identified as caused by various Coxsackie viruses. Although the cause of the "common cold" has not been revealed by any of the workers in this conference, the causative agents of many of the "uncommon colds" have been identified.

Finally, all the various situations now recognized for bacterial infections have also been found to be applicable to these new groups of viruses. Some persons may become infected with certain viruses, with the production of symptoms of varying degrees of severity. Others may have subclinical infections caused by the same agents, as evidenced by the production of antibodies specific for those agents. Still others may yield the viruses either with or without manifest disease, but fail to develop demonstrable antibodies or, having previously been exposed to an immunizing infection, may continue to harbor and excrete the virus as carriers.

It is abundantly clear from the proceedings of this conference that the high quality and intensive industry of the workers in this field have yielded a great deal of important information that is now being organized in an intelligent and useful manner. The organization and application of the knowledge thus acquired should eventually help the clinician to identify specific entities and should advance the search for methods of attack on these diseases, either through chemotherapy or by prevention through the use of vaccines. These, in turn, may eventually lead to the control of some important entities in which some of the newly discovered viruses play a major part.

A CHANGE OF PACE

HARVARD Medical School loses this summer by retirement, through the orderly but inevitable processes of chronologic progress, two of its most eminent full professors.

Dr. Joseph C. Aub, professor of research medicine at the University, chairman of the Department of Medicine at the Medical School and director of the School's laboratories in the Collis P. Huntington Memorial Hospital, will relinquish these posts to become professor of research medicine, emeritus. Dr. Aub's early investigations into basal metabolism led to vital information regarding lead poisoning; as a member of the Cancer Commission of Harvard University he has been mainly concerned with the roles played by the glands of internal secretion in the control of cell growth.

Dr. Aub was appointed physician-in-chief at the Huntington Hospital and a member of the Cancer Commission in 1928. He has been physician at the Massachusetts General Hospital since 1942 and professor of research medicine since 1943.

Dr. Harry C. Solomon will retire as professor of psychiatry at Harvard University, becoming professor emeritus, but will continue as medical director of the Boston Psychopathic Hospital, now the Massa-

chusetts Mental Health Center and Boston Psychopathic Hospital. Dr. Solomon, an international leader in the field of psychiatry, has helped shape the modern teaching of psychiatry during its emergence as a distinct medical discipline.

A native of Nebraska, Dr. Solomon received his academic training in California and his medical instruction at Harvard Medical School, from which he graduated in 1914. President of the Association for Research in Nervous and Mental Disease, he is president-elect of the American Psychiatric Association and past-president of the American Neurological Association and the Society of Biological Psychiatry.

It may be anticipated that academic retirement will be the prelude to a new phase of productivity on the part of these distinguished scholars.

Intermarriage.—*In the little town of Wick, England, there are forty-two insane persons. Their imbecility is said to be caused by want of nourishing diet and by frequent intermarriage among relations.*

Boston M. & S. J. *July 17, 1856*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Uterine Atony and Post-Partum Hemorrhage

A thirty-three-year-old gravida 3, para 2, entered the hospital in active labor twelve days after the estimated date of confinement. The blood pressure on admission was 138 systolic, 90 diastolic. Two hours later, under light open-drop ether anesthesia, a normal infant weighing 3.2 kg. (7 pounds, 1 ounce) was delivered by outlet forceps and mediolateral episiotomy. Ergotrate was given intravenously with delivery of the infant, and was repeated five minutes later (at 6:30 a.m.) with delivery of the intact placenta. On completion of the third stage, the patient was bleeding more than normally, and several large clots were expressed from the large, softened fundus. However, the attending physician did not consider the blood loss alarming or excessive, estimating the entire loss at 700 ml. on one occasion and "not over 500 ml." on another. At 6:40, because bleeding continued and the fundus stayed soft, 1000 ml. of 5 per cent dextrose in water, with 1 ampoule of Pitocin, was started intravenously. The pulse was weak and rapid, and the blood pressure could not be obtained. The patient was thrashing about and restless. At 6:45 a transfusion was ordered, and oxygen begun. By 7:00 no pulse was obtainable. Some bleeding continued, and small clots were expressed from the fundus. Respirations were weak, gasping and rapid. Cardiac stimulants and artificial respiration were without avail, and the patient was pronounced dead at 7:25, an hour after delivery, and before transfusion had been started. In the absence of an autopsy the death was signed out as due to a cerebrovascular accident.

This case was classified as a preventable death due to uterine atony and post-partum hemorrhage. The primary avoidable factor was failure to give a transfusion.

Although absolute diagnosis cannot be proved without an autopsy, there were no convincing signs of a sudden neurologic disaster. On the contrary there was considerable evidence of profound blood loss, such as air hunger, restlessness, weak, gasping respirations, rapid pulse, and absent blood pressure, not long after expression of the placenta was followed by failure of the uterus to contract. Although the bleeding was not deemed excessive at the time, an estimate of 700 and later of 500 ml. was made, and bleeding was described as "more than normal." Fifteen minutes later, glucose and Pitocin were given intravenously, and shortly afterward a transfusion was ordered but, presumably, could not be started in forty minutes. One is driven to the conclusion that an honest but unfortunate underestimate of blood loss must have been made. This is so frequent as to be tragic. No hemoglobin recordings are available for the patient during her prenatal course (this in itself merits criticism), but it is worth mentioning that moderate to severe secondary anemia is extremely common during the third trimester of pregnancy, and when this exists blood loss need not be apparently "excessive" to be fatal. What is lost on drapes, sponges and in the waste receptacle can never be accurately assessed, and actual blood loss is frequently two or three times the conservative clinical estimate. Under the circumstances, the only thing that could possibly have saved this patient would have been copious transfusion, begun immediately when bleeding in the third stage was found to be more than "normal." The intravenous infusions of fluids and Pitocin were good, but too late, and fluid alone is never more than a stopgap for hemorrhage. A bottle of blood kept constantly on the delivery floor by rotation from the main bank could conceivably have staved off this disaster.

John Figgis Jewett, M.D.
Chairman

DEATH

MACDONALD — William C. MacDonald, M.D., of Malden, died on June 24. He was in his ninety-first year.

Dr. MacDonald received his degree from the University of Colorado School of Medicine in 1895.

He was chairman emeritus of the medical board at Malden Hospital.

He is survived by his widow, six daughters and two sons.

CORRESPONDENCE

CARE OF MILITARY PERSONNEL AWOL

To the Editor: In a number of cases physicians and hospitals have accepted for emergency treatment members of the Army who were in a status of absent without official leave (AWOL). Upon subsequent submission of vouchers for payment, the physician or hospital has had to be informed that current regulations preclude the payment from public funds for medical treatment rendered military personnel in such a status.

In an effort to inform interested persons of the means whereby payment may be authorized for emergency treatment of a person who is first seen in an AWOL status, it is believed that the proper procedure should be publicized through state journals.

Upon the acceptance by a hospital or physician of a member of the military service (Army, Navy or Air Force), immediate report should be made to the nearest military facility of the illness or injury. This procedure should be accomplished whether the person is absent with or without official leave in order that his parent organization may be informed of his continued absence by reason of illness or injury. If he is in an AWOL status, the report of his location and illness or injury constitutes a return to military control and in effect terminates his AWOL status. The Government subsequently becomes responsible for payment of his medical care by civilian agencies. These statements apply to practically every situation except unusual cases in which a person is engaged in a criminal act or when unauthorized medical care is furnished for a condition that is not an emergency. Also, the assumption must be made that one service will act for the other in the matter of relaying the information to the parent organization.

Statements of account for payment may be forwarded to the commanding officer, who will transmit them to their proper destination. The processing of an account involves a matter of weeks, but payment is certain when emergency medical care is rendered a bona fide member of the military service who is not AWOL and who is not engaged in a criminal act.

Further information may be obtained from the Surgeon, First Army, Governors Island, New York.

H. W. GLATTLY
Brigadier General, MC
Surgeon
Headquarters, First Army
Governors Island, New York

SUSPENSION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held June 7, 1956, it was voted to suspend the registration of Dr. John D. Latorella, 305 Chelsea Street, East Boston, for five months beginning October 1, 1956.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

BOOK REVIEWS

Cardiac Diagnosis: A physiologic approach. By Robert F. Rushmer, M.D. 4°, cloth, 447 pp., with illustrations. Philadelphia: W. B. Saunders Company, 1955. $11.50.

This book, which presents a unique approach to cardiac diagnosis that is exceedingly important in view of the many recent contributions to the physiology of the cardiovascular system, is divided into five parts. The first is composed of an authoritative discussion of the anatomy and the physical and functional aspects of the cardiovascular system. The second concerns the neural and hormonal regulation of the same. The third deals with congestive heart failure. The fourth presents a comprehensive review of old and new diagnostic technics. The fifth is an attempt to correlate the various diagnostic procedures with the main types of heart disease.

Especially useful is the wealth of informative illustrations, with complete legends, which are beautifully reproduced. By this simple device, many phenomena that are somewhat complicated when studied by the ordinary written word are made clear and easily understandable. These alone make the volume a worth-while addition to any physician's library.

The author carefully avoids tedious presentations of various controversial subjects. An adequate bibliography is provided for those who wish to delve further into any particular subject.

I should have liked a more thorough presentation of the clinical aspect of heart disease, such as a discussion of history, symptoms and physical findings, since I find it difficult to dissociate this from cardiac diagnosis, in spite of all the useful laboratory procedures.

The book is not intended to be a comprehensive discourse on cardiac disease. Nevertheless, here is a great deal of useful information, clearly presented, that should appeal to the beginning student of cardiology, as well as the experienced practitioner.

DAVID I. RUTLEDGE, M.D.

Glaucoma: A symposium organized by the Council for International Organizations of Medical Sciences: Established under the joint auspices of UNESCO and WHO. Edited by Sir Stewart Duke-Elder, England. 8°, cloth, 350 pp., with illustrations, tables, charts and a frontispiece. Springfield, Illinois: Charles C Thomas, 1955. $7.50.

This is an investigator's symposium brought about largely through the intensification of interest in glaucoma that has resulted from recent developments of new technics and methods of investigation.

The disease under discussion has claimed attention because of its status as a leading cause of blindness in adults. It has long been known to be characterized by the abnormally high pressure of the intraocular fluids, but only during the past decade and a half has a coherent concept been evolved concerning the mechanisms of formation and escape of the fluid. From among the scientists and clinicians most closely concerned in elucidating these mechanisms, 20 representatives were brought together from several countries for this symposium. From the published proceedings it is evident that the occasion has served well to advance understanding and harmony of purpose among the participants, and the friendly atmosphere present at the actual conference has been well preserved. One result has been an achievement of unanimous agreement on the existence of at least two distinct types of primary glaucoma that have different pathogeneses and require different forms of treatment.

In the arrangement of program, editing and summing up of discussion the celebrated organizational ability of Sir Stewart Duke-Elder is quite evident. The record offers interesting and informative reading for ophthalmologists and others interested in the anatomy, physiology and pharmacology of the eye, as well as in the disease itself.

W. MORTON GRANT, M.D.

NOTICES

INTERNATIONAL CANCER CYTOLOGY CONGRESS

The first international congress in the field of cancer cytology, sponsored by the College of American Pathologists, the Intersociety Cytology Council and the American Society of Clinical Pathologists, will be held at the Drake Hotel, Chicago, Illinois, October 8 through 13. Three sponsoring organizations will hold their annual meeting on the following evenings: College of American Pathologists on Monday, October 8; Intersociety Cytology Council on Wednesday, October 10; and American Society of Clinical Pathologists on Thursday, October 11. The general theme of the congress will be "Exfoliative Cytology." Further information may be obtained from Dr. A. H. Dearing, Executive Secretary, College of American Pathologists, Prudential Plaza, Chicago, Illinois.

SOCIETY MEETINGS AND CONFERENCES

July 17–August 28. Consultation Clinics for Crippled Children in Massachusetts. Page 1244, issue of June 28.
August 19–23. American College of Chest Physicians. Page 840, issue of November 10.
September 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
September 10–14. American Dietetic Association. Page 1180, issue of December 29.
October 8–13. International Cancer Cytology Congress. Notice above.
October 19 and December 14, 1956, and February and April, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
October 30 and 31 and November 1. New England Postgraduate Assembly, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JULY 19

THURSDAY, JULY 19
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Yamins A, Beth Israel Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Mitral Valvuloplasty in Patients over Fifty. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, JULY 20
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, JULY 21
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, JULY 23
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.

TUESDAY, JULY 24
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, JULY 25
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathologic Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.